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Aluminium Poisoning with Analytical aspects and its Management

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ABSTRACT: Aluminium is the thirteenth element of periodic table with molecular mass of 26.98 units. It is the third most abundant element in earth's crust and is ubiquitously distributed making up to 8 % of total core mass of earth. It binds easily with other elements hence pure form of aluminium is not found in nature. Aluminium generally does not cause any toxicity or poisoning until the individual is exposed to large amounts and for longer duration of time. Its poisoning can be caused by three ways which includes ingestion, inhalation and dermal contact. Aluminium is found in various consumer products, hence it is found in all tissues of human body. In a normal healthy individual, the total body burden of aluminium is estimated to be 30 to 50 mg. It targets the major organs of body such as lungs, CNS and bones. It is known to compete with cations in biological systems of body, especially magnesium, in order to bind with transferrin and citrate in blood. The biological samples urine, blood, serum, bone and other tissues are frequently used for detection of aluminium poisoning. The various aspects along with the treatment and hospital management have been reviewed in this paper based on the reported aluminium poisoning. Other than that, the analytical techniques which include ICP-MS, AMS, GFAAS, ICP-OES are also discussed which are used routinely in the diagnosis of heavy metal toxicity.

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INTRODUCTION:

Aluminium is a silvery-white, ductile, soft, highly conductive and corrosion resistant metal derived from the bauxite ore. It easily binds to other elements, hence, pure form of aluminium does not exist in nature. Bauxite is the chief ore of aluminium, which is the combination of hydrated aluminium oxides. It has three valence states, out of which +3 (Al_2O_3) is most common whereas +2 and +1 are less common. There are nine isotopes of aluminium ranging from mass number 23 to 30. Al^{27} is

referred as stable isotope whereas Al^{26} is the radioactive one, existing in the nature. From practical point of view, these isotopes are being used in dating glacial ice, marine sediments, in isolation of quartz from rock and in determining the terrestrial age of meteorites [1].

Aluminium generally does not cause any toxicity or poisoning until the individual is exposed to large amounts and for longer duration of time. Air and water concentration of aluminium varies from place to place, higher in those regions where aluminium related industries are in existence. Whereas poisoning through inhalation occurs to the workers working in industries such as refining, mining, smelting, and those which are involved in production of tools by the process of grinding and cutting using aluminium metal or its compounds. Poisoning can be caused by three ways which includes:

- By ingestion of too much Al through food and water.
- By inhalation of too much Al in lungs.
- By constant contact with the skin.

Because of its peculiar chemical properties, Al forms number of compounds such as aluminium hydroxide, aluminium oxide, aluminium chlorohydrate, aluminium lactate, aluminium chloride, aluminium phosphate and aluminium nitrate. There is an exception in case of aluminium phosphide where the anionic part does not seem to cause toxicity, however it does seem to influence the bioavailability. Aluminium phosphide is generally used as pesticide and it is much more lethal compared to other forms but this is due to the production of phosphine gas which is a potent systemic and respiratory system toxin, not due to the exposure to aluminium [1-3].

Aluminium exposure has negative influence on the major organ systems of body such as respiratory system, CNS and skeletal system. It has been reported that Al competes with cations in biological systems of body, especially magnesium in order to bind to transferrin and citrate in blood. Common biological samples like urine, blood, serum, bone and other tissues are frequently used to investigate the aluminium toxicity [3].

SOURCES OF ALUMINIUM:

- Its alloys are vital to the aerospace industry and building industries [4].
- It is used in making of utensils.
- It is used in making electrical equipment, packaging and making automobiles.
- Powder of aluminium is used in paints and pigments.
- Used in fuel additives, propellants and explosives.
- Oxides of aluminium are used as additives in food.
- Aluminium oxides are also used in manufacturing of ceramics, catalysts, electrical insulators, light bulbs, spark plugs, abrasives, artificial gems and heat resistant fibers.
- Aluminium hydroxide is commonly used in products of personal care.
- It is used as preservatives, fillers, coloring agents, emulsifiers and baking powders in food.
- Zeolite and Bentonite, naturally occurring aluminium minerals are used in sugar refining, water purification, paper and brewing industries [1,5].
- It is also used in making coal fixed power plants and incinerators.
- Aluminium salts are used as adjuvants in preparations for vaccines and hypo-sensitization.

EXPOSURE OF ALUMINIUM:

Humans can get exposed to aluminium and its compound through variety of ways:

- It can occur due to contamination of water and air, depending upon the aluminium industries present in that particular area.
- It is one of the integral parts of several aerosol formulations of cosmetics, which when used on regular basis for longer time will significantly contribute to the exposure through inhalation and transdermal absorption.
- Using aluminium containing antacids with 300 to 600 mg of aluminum hydroxide which have approximately 104 to 208 mg of Al per tablet, or 5 ml of liquid dose for longer duration can cause its toxicity.
- Aluminium is crustal by its origin, therefore at the uncontaminated places the surface of soil contains a source of aluminium species in the surface water, in sediments and ambient air aerosols.
- Workers working in the industries like refining, mining, smelting, and those which make tools by grinding and cutting using metal or compounds of aluminium are routinely exposed to aluminium and can cause its toxicity.

Other sources may include aluminium utensils which are used for the purpose of cooking.

All the above depend on various factors such as amount of exposure, duration of exposure, type of exposure along with the lifestyle, age, sex, diet and health status of individual [1,5].

PHARMACOKINETICS OF ALUMINIUM:

Absorption:

The absorption of aluminium is very less in body through ingestion or inhalation and it is very poor in case of dermal exposure. Nearly 0.1 to 0.6 % of aluminum is absorbed through ingestion whereas absorption of less bioavailable form such as aluminium hydroxide is as low as 0.1 % and the rest is excreted in feces. The bioavailability depends on the compound and the availability of dietary components which can form complexes with aluminium that may or may not enhance its binding and absorption. Aluminium inhaled through air is absorbed via lungs, GI tract following mucociliary clearance from the respiratory system, or it can absorb via intranasal olfactory neurons. After that it may enter the brain either directly or via olfactory tract or cross nasal epithelium by axonal transport. Absorption of aluminium through food and water is very less because it depends on the bioavailability of its compounds. Similarly, dermal absorption can occur by using cosmetic products especially antiperspirants containing aluminium carbohydrate which is known to block the sweat duct by aluminium hydroxide. After entering the blood stream, it binds to various ligands and gets distributed in each organ system of the body with highest concentration in lungs and bones tissues. Aluminum has the capability to form complexes with various molecules in the body [6].

Distribution:

Normally it is found in all the body tissues. In a normal healthy individual the total body burden of aluminium is approximately 30 to 50 mg. The levels of aluminium in serum is 1 to 3 µg/l. Half the total body burden of aluminium is in bones, one fourth in lungs and rest in other tissues of body. Food is the major source of aluminium in all body parts, normal range of aluminium in bone tissues is 5 to 10 mg/kg. It is also found in lower GI tract, skin, lymph nodes, parathyroid and adrenal glands. In the brain the gray matter contains double the amount of aluminium than found in white matter. With the increase in age, the concentration of aluminium also increases in brain tissues and serum. As soon as body through inhalation, it gets distributed in lungs based on their particle size, some portion gets exhaled, some gets accumulated in nasopharyngeal and upper areas of respiratory tract and few gets deposited in gastrointestinal tract by mucociliary action. Out of all only a small portion will reach the alveoli and gets transferred to either blood (soluble compounds) or to alveolar macrophages by phagocytosis followed by transportation to lymph nodes (insoluble compounds). After getting into blood stream it binds with transferrin in serum. Apart from transferrin it also binds with bone tissues, predominately in metabolically active parts of bone. Higher levels of aluminium and its compounds are also visible in fetus which suggests its transplacental transfer [6].

Elimination:

The unabsorbed aluminium gets eliminated from the body through feces, whereas the absorbed aluminium gets eliminated through kidneys or urine. After prolonged exposure of Al and its accumulation, human body itself is not capable of eliminating aluminium and its compounds effectively from the body [6].

MECHANISM OF TOXICITY:

The mechanism includes targeting the major organs of body such as lungs, CNS and bones. It is known to compete with cations in biological systems of the body, especially magnesium to bind to transferrin and citrate in blood. It might affect calcium availability through its binding to nuclear components irreversibly, thereby affecting secondary messenger systems. It might inhibit neuronal microtubule production. In bones it causes osteomalacia and rickets by inhibiting the absorption of dietary phosphorus [2].

ONSET AND DURATION OF ACTION:

The symptoms of aluminium toxicity depend upon the duration and amount of exposure. However, it may take weeks to months for the symptoms to appear, depending upon the dose and compound of aluminium until one swallows the large amount all at once [6].

FATAL DOSE AND FATAL PERIOD:

Intake of 40 mg/kg of body weight will result in the symptoms of aluminium toxicity. More than 70 mg/kg of body weight will lead to severe poisoning within few months of intake [5].

NORMAL AND REFERENCE VALUES:

In normal unexposed individuals the range of aluminium concentration lies between 7 µg/l to 10 µg/l in blood and less than 7 µg/l in urine (Table 1). More than 60 µg/l can lead to aluminium toxicity [7, 8]. The tolerable weekly intake of aluminium set by the European Food Safety Authority is 1 mg Al/kg body weight [9]. The SRL (Specific Release Limits) reports specifies, the maximal

amount of metal ions (in mg) that may be transferred from a defined surface of the contact material to the food (in kg) or food simulant is 5 mg/kg food stuff [10].

Table 1. Normal levels and reference toxic values of Aluminium.

Matrixes	Normal Level	Toxic Level
Blood	7 to 10 µg/l	> 60 µg/l
Urine	< 7µg/l	30 to 100 µg/l
Serum	1 to 3 µg/l	50 to 100 µg/l

SYSTEMIC EFFECTS OF ALUMINIUM ON BODY:

Respiratory effects:

These effects are generally seen in people who are working in potrooms, foundaries and in welding operations where the workers are exposed to the fumes, dust and powdered forms of aluminium. Apart from aluminium these people are also prone to various other chemicals which are toxic to body such as Sulphur dioxide, carbon monoxide, hydrogen fluoride, chlorine, polycyclic aromatic hydrocarbons (PAHs) etc. The effects include wheezing, impaired lung function, dyspnea and occupational asthma. Pulmonary fibrosis is one of the most commonly seen detrimental effects due to the exposure through inhalation. In some cases, aluminium induced pneumoconiosis, interstitial pneumonia, pulmonary alveolar proteinosis and granulomas are also reported [11].

Cardiovascular effects:

Hypertrophy and dilation may be seen in the parts of heart in case of inhalation of large amount of aluminium powder. It may also include secondary to pulmonary fibrosis and decreased pulmonary function. There are also report of increase in erythrocyte sedimentation rates and a decrease in RBC's hemoglobin content due to aluminum poisoning. Based on rodent studies, long-term Al exposure induced dose-dependent bioaccumulation, genomic DNA oxidation, micromineral imbalance, structural and ultrastructural disturbances in the cardiac tissue, thereby resulting in extensive parenchymal loss, diffuse inflammatory infiltrate, increased collagen deposition, reduced myocardial vascularization index, mitochondrial swelling, sarcomere disorganization, myofilament dissociation, and fragmentation in cardiomyocytes [11].

Effects on Bones:

According to International Commission on Radiological Protection, the skeleton contains the major portion of aluminium in body tissues, accounting for 54% of the total aluminium content of body. It is considered toxic to major body organs including bones in which it can cause softening of bones and loss of bone mass which results in osteomalacia followed by fracturing osteodystrophy. Aluminium can be retained in bones for longer duration with a half-life of approximately 10 to 20 years. Aluminium gets accumulated in skeleton tissues because of the transfer of Al ions from citrate and transferrin to blood and then to bone surfaces, along with internal endosteal surface, external periosteal surface, surface of vascular channels and trabecular surface which permeate compact bones. The chronic effects include dynamic bone disease in which the process of bone formation is disrupted leading to spontaneous fractures. Aluminium has also been seen to bind with secretory granules proteins leading to disruption in the process of exocytosis followed by inhibiting the release of parathyroid hormone containing secretory granules which results in hypoparathyroidism [11].

Neurological Effects:

Some studies show that aluminium ions which does not undergo redox reaction might provoke oxidative changes and activate the production of reactive oxygen species, which can cause various neurodegenerative disorders particularly Alzheimer's disease. In some cases, accumulation of aluminium may initiate inflammatory processes followed by induction of synthesis and release of interleukins and other inflammatory cytokines [2].

Breast Cancer:

Due to inadequate and disputable data, the relationship of aluminium and breast cancer can neither be explicitly substantiated or negated. It has been observed that breast tissue of women with tumors to some extent may exhibit higher aluminum concentrations than tissue from healthy women. However, the data related to this are contradictory and as of now, it is not possible to draw scientifically tenable conclusions regarding antitranspirants or deodorants containing aluminum and breast cancer. The aluminum-free antitranspirants are commercially available [12].

ANALYTICAL TESTS FOR ALUMINIUM POISONING:

Qualitative analysis of Aluminium Poisoning:

***Aluminon Reagent Test*:**

- Ammonia solution is added to 1 ml of extract.
- White gelatinous precipitate appears.

- The precipitate is taken in a micro test tube and 2M HCl is added to dissolve it.
- To this, 1 ml of 10M ammonium acetate and 2 ml of 0.1% aqueous solution of the aluminon reagent is added.
- Ammonical ammonium acetate solution is added in excess to decolorize the dyestuff and prevent interference of chromium, silica, etc.
- A bright red precipitate appears, which confirms the presence of aluminum.

***Alizarin Reagent Test*:**

- One ml of the extract is placed on a spot plate.
- One drop of the alizarin reagent is added.
- Then acetic acid is added drop wise, until violet color disappears.
- One drop of acid is then added to it.
- A red precipitate is observed indicating the presence of aluminum.

Quantitative analysis of Aluminium Poisoning:

Various methods used to detect the levels of aluminium in biological samples are as follows:

***Accelerator Mass Spectroscopy (AMS)*:**

- AMS is one of the precision techniques that can determine the accurate levels of aluminium from few milligrams of the sample.
- It utilizes a particle accelerator having an ion source, large magnets and a detector. The detection limit is one atom in 10^{15} that is one part per quadrillion (ppq).
- The analysis begins with extraction of aluminium from biological sample by using a method free from contamination followed by loading of extractant into a holder and inserting it into the ion source through a vacuum lock which further bombards the sample to ionize the atoms.
- These ionized atoms are extracted from the sample using magnets and are separated by accelerators, bending magnets and electron stripper screens based on their mass and charge.
- On the basis of rate of energy loss, there is differentiation between competing isobars and gas ionization detector counts the ions one by one.
- The measured ratio of Al^{26} to Al^{27} and the concentration of carrier used during sample preparation is used to calculate the level of Al^{26} in the sample [2].

***Graphite Furnace Atomic Absorption Spectrometry (GFAAS)*:**

- It is widely used analytical technique for detection of aluminium even at low concentrations like in parts per billion from whole blood, serum, urine, plasma and biological tissues.
- It offers high sensitivity, cost efficiency and simplicity.
- It can be used as a detector for HPLC which can offer analysis of complexes of Al or bound form Al species that are separated into fractions on the column [2].

***Inductively Coupled Plasma Optical Emission Spectrometry (ICP- OES)*:**

- ICP - OES relies on the spontaneous discharge of light with specific wavelength from ions and atoms already excited in plasma.
- A photo detector is used to convert the wavelength into electrical signal.
- The sample is injected into the central channel of plasma core which is at a temperature of approximately 10000 ˚C after its conversion into an aerosol.
- A complete Atomization of sample occurs in argon plasma, which helps in minimizing the interferences.
- The detection limit for aluminium in blood and urine is 1 to 4 µg/l.
- One major disadvantage of using this technique is the broad emission of calcium, which heightens the background and also increases the detection limit of aluminium [2].

***Neutron Activation Analysis (NAA)*:**

- NAA uses the neutrons to bombard the sample, which changes few of the stable atoms of Al^{27} into radioactive isotopes of aluminium starting from Al^{28} followed by calculation of induced radioactivity.
- It has several advantages which include high sensitivity, independence from interferences and matrix effects.
- However, disadvantages of using NAA are its high cost, disposal of radioactive waste, short half-life of isotope and the major problem is that phosphorus and silicon also produces the same radioactive isotope as that of Al^{28} which can offer interferences to aluminium [2].

***Inductively coupled plasma-mass spectrometry (ICP-MS)*:**

- This technique utilizes an ion source of inductively coupled plasma and mass spectrometer as ion analyzer.
- The detection limit of aluminium for blood and urine is reported to be 0.02 µg/ml.
- It can also be used as a detector for fractions separated with size exclusion chromatography with the detection limits of 0.04 µg/g in kidneys, brain and femur bone [2].

SYMPTOMS / CLINICAL FEATURES IN ALUMINIUM POISONING:

Symptoms of Al toxicity mostly depends on the type, time of exposure and amount of dose. The most threatening toxicity occurs due to inhalation of high doses of aluminium, which generally occurs to people residing in industrial areas.

Symptoms of acute poisoning:

- Confusion.
- Muscle weakness.
- Seizures.
- Speech problems.
- Bone deformities and fractures.
- Shunted or slow growth in children.
- Asthma.

Symptoms of chronic poisoning:

- Lungs related problems.
- Bone disease.
- Anaemia.
- Impaired absorption of iron.
- Neurodegenerative disease such as Alzheimer's disease.
- CNS related issues.
- Osteomalacia [5].

DIAGNOSTIC INVESTIGATION:

The diagnosis of aluminium toxicity depends upon the combination of both the clinical history of patient and the laboratory findings.

- The specimens to be tested includes whole blood sample, bone tissue, stool or urine.
- By measuring the concentration of aluminium in blood and urine information about the duration of exposure and amount of exposure can be extracted.
- Whereas, concentration of aluminium in bone can provide information about high levels of exposure of aluminium.
- In case of lung involvement X- rays and ECG is performed.
- The lab test utilises ICP-MS and AMS detection method [13,14].

MANAGEMENT/TREATMENT:

As soon as the diagnosis is confirmed the treatment should be initiated to avoid further irreversible damage to the patient. Criteria of management in Aluminium poisoning includes.

Home Care:

Exposure of small amount of aluminium does not cause toxicity but if it does, leave the area of exposure and get some fresh air. Eliminate aluminium from the food or diet, medications and antiperspirants. Wash the area of skin with water if skin comes in contact with it.

Observation at hospital:

In case the exposure is for longer time and of large amount, consult the doctor. Although the symptoms after longer exposure are hardly reversible, the patient has to take the medication for longer duration.

***Criteria for toxicologist consultation*:**

The physician in case of systemic toxicity can consult the toxicologist or poison control centre for more details [2].

***Hospital Management*:**

- It starts with complete and thorough examination of the patient which includes serum level of aluminium, hepatic function, whole blood test, renal function test and coagulation profile.
- In case of swelling and inflammation in lungs, blood, urine tests, ECG and X- rays are performed.
- In some rare cases of heavy aluminium poisoning haemodialysis is performed and antidote is given to reverse the effects.
- Chelation therapy is one of the most efficient techniques used for treating aluminium poisoning. Metal ions form stable complexes with chelators. Chelators often work by reducing the absorption and distribution of aluminium in body especially to the sensitive organs or targets such as brain. Most commonly used chelator in aluminium poisoning is Desferrioxime (DFO). However, DFO has limited clinical usefulness due to its toxic effects. Other chelators are 1,2-dimethyl-3-hydroxypyrid-4-one and (4-methyl-6-trifluoromethyl-6-pyrimidin-2-il)-hydrazine.

- While performing the therapy, the concentration of aluminium increases in blood and after the therapy the concentration decreases in blood and increases in urine.
- The DFO is given intravenously at a dose of 5mg/kg/week for adults. The dose is given in case of chronic poisoning and can be increased in case of severe aluminium toxicity [14,15].

CONCLUSION:

Toxicity of aluminium is a result of prolonged exposure to large amount of aluminium and its compounds, so it is highly important to avoid direct contact with the metal. Once exposed, it has the potential of entering into the bloodstream, thereby affecting the major organ systems of the body. Various tests are being performed to detect its toxicity using blood, bone tissue or urine. ICP-MS is the method of choice which confirms the poisoning caused by aluminium. After the diagnosis proper treatment should be given to the patients which include chelation therapy at the hospital.

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