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REVIEW ARTICLE

COBALT TOXICITY/POISONING WITH ANALYTICAL ASPECTS AND ITS MANAGEMENT

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ABSTRACT: Cobalt is one of the essential Components found in trace amounts in human beings, has an atomic number of 27, molecular mass of 58.93 units and represented by the symbol Co. It is important for the formation of Cyanocobalamin or Vitamin B_{12}. Normally a healthy diet contains 5 to 50µg of cobalt in a day. Cobalt generally does not cause any toxicity or poisoning until the exposed to large amounts and for longer time period. Poisoning can be caused by three ways which include- Swallowing too much, inhaled too much in lungs and constant contact with the skin. Various effects are visible in case of cobalt poisoning which includes cardiovascular effects, neurological, haematological, immunological, dermatological, ophthalmological, gastrointestinal and reproductive system dysfunction. The biological samples which are analysed for cobalt poisoning includes urine, blood, serum and tissues. The various aspects along with the treatment and hospital management is discussed in this paper. Other than that, the analytical techniques which include HR-ICP-MS, XRF, UV Spectrophotometry, ICP-OES are also discussed which are used in the diagnosis.

KEY WORDS: Cobalt toxicity, Cyanocobalamin, HR-ICP-MS, XRF, ICP-OES etc.

INTRODUCTION:

Cobalt is a rare element of earth's crust which is essential to mammals in the form of cynacobalamin.[1] Cobalt-59 is the one naturally formed isotope of cobalt and also it has ten radioactive isotopes known till now. Out of all Cobalt-60 is the one used for the treatment of diseases like *Schilling test*, which detects the deficiency of vitamin B_{12} efficiently. Along with that it also helps in the treatment of Cancer by using radiations to destroy cancerous cells. It is important for the formation of Cyanocobalamin or Vitamin B-. Normally a healthy diet contains 5 to 50µg of cobalt in a day. Now a days this metal is used for various purposes which includes medicinal, recreational and scientific ones. Medically, used in orthopaedic implants as alloys and superalloys. Scientifically as oxidation catalysts for chemical reactions. The three

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major catalysts are Dimethylterephthalate (DMT), Terephthalic acid (TPA) and cobalt acetate along with manganese; DMT and TPA are used for the production of resin used to make plastic bottles and new ultra-strong plastics; Hydro-treating, desulphurisation- cobalt molybdenum oxide-CoMOX used for gases and oils; and Oxo (O^{2-} ligands) catalysts- freshly reduced cobalt metal or cobalt salts. And recreationally, for colouring and pigments which gives blue tint to glass [2].

Cobalt generally does not cause any toxicity or poisoning until the exposed to large amounts and for longer time period. Air and water concentration of cobalt varies from place to place, higher in places having cobalt related industries. Whereas poisoning through inhalation occurs to the workers working in industries which include refining, mining, smelting, and those that make tools by grinding and cutting using cobalt metal or compounds of cobalt. Poisoning can be caused by three ways which include-

- By Swallowing too much,
- By Inhaled too much in lungs,
- By Constant contact with the skin.

These days poisoning can also be caused due to the wear and tear of some chromium/ cobalt metal-on-metal hip implants. The implant is made using a hip metal ball fitted into a metal cup forming an artificial socket of hip. Due to the friction between the two surfaces while walking, some particles are released which sometimes enters the bloodstream causing poisoning of cobalt. Poisoning may be associated with polyneuropathy, eye and auditory nerve damage, hypothyroidism and cardiomyopathy. Therefore, symptoms along with suitable diagnosis and treatment are highly valuable in cobalt poisoning cases. [2]

SOURCES OF COBALT

Major sources of Cobalt are as follows–

- It is found in some metal-on-metal hip implants.
- It is found in batteries as Lithium cobalt oxide.
- It is found in colouring pigments and dyes as cobalt blue.
- It is found in saw blades, drill bits and other tools used in machines.
- It forms alloys with chromium, nickel, molybdenum, tungsten etc.
- It is found in Magnets.
- Earlier cobalt was used as a stabilizer in foam of beer which causes the condition known as beer drinker's heart disease, resulting into cardiac muscle weakness.
- Cobalt forms a major component of Vitamin B_{12}.

EXPOSURE OF COBALT

- It can occur due to contamination of water and air, depending upon the cobalt industries present in that area, as it can cause cancer of various body parts.
- It can occur due to the metal-on-metal prosthetics used by patients.
- It can occur due to the overdose of vitamin supplements of vitamin B_{12}.
- It can occur to the workers working in industries which include refining, mining, smelting, and those that make tools by grinding and cutting using cobalt metal or compounds of cobalt.
- An individual having radiation therapy is highly exposed to cobalt as it can produce various ill effects to health including lower white blood count, bleeding, diarrhoea, sterility, coma and even death in few cases of longer exposure.

All these effects totally depend on various factors which include amount of exposure, duration of exposure, type of exposure along with the lifestyle, age, sex, and diet and health status of individual.

PHARMACO-KINETICS OF COBALT

Absorption

There are few ways by which cobalt enters the body. The cobalt entering the body through food is absorbed at small intestine, followed by absorption of metal into blood flow where it causes the binding with proteins and transportation to various cells of body resulting in accumulation in all organs mainly includes liver, pancreas, kidneys, heart and skeletal muscles. Cobalt particles entering through inhalation gets through to the lower and upper tract of respiratory system based on the size of particles. Larger ones are swallowed and go to the oesophagus and the smaller ones passes through the endothelial cells to lungs resulting in various diseases such as asthma, rhinitis, inflammation and a higher risk of cancer in lungs. Direct and longer contact to skin may result in allergic contact dermatitis and repeated contact can also cause diffusion through skin can lead to allergy and irritant reaction. [3]

Distribution

Since cobalt is a major component of vitamin B_{12}, it is found in most body tissues like bone, hair, lungs, muscle, lymph nodes, brain, pancreas, liver (largest amount), urinary bladder etc. reflecting the exposure from all sources and routes. Normally in humans, total body burden is estimated as 1.1-1.5 mg with 0.11mg in liver. Whereas lung concentration of cobalt is higher in workers working in mining and smelting industries. [4]

Elimination

Long term clearance is directly related to the solubility of cobalt compound, e.g., higher (cobalt (II) oxide) the solubility faster the clearance from lungs than the less soluble ones (cobalt (III) oxide). Soluble ones are absorbed in the blood at faster rate and are eliminated through the faeces and urine. Faecal excretion occurs in case of oral exposure. [4]

MECHANISM OF ACTION/ TOXICITY

As soon as cobalt enters the bloodstream it binds with the blood plasma proteins and circulated to various tissues which further gives rise to the reactive oxygen species which cause harmful effects to the body as it reaches various organs. Some hard metal particles have the ability to form substantial amounts of oxidant species which cause lipid peroxidation. It also has the ability to form free radicals which can cause damage to DNA. Soluble cobalt has the potential to block the calcium channels. In some cases, it causes inhibition of major enzymes of mitochondrial oxidative phosphorylation, inhibition of thyroid iodinase and direct cytotoxicity. Organs which are exposed to the toxicity of cobalt includes liver, lungs, pancreas, cardiovascular system and kidneys. [2, 5]

ONSET AND DURATION OF ACTION

The symptoms of cobalt 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 cobalt until one swallow large amount at once. Symptoms of toxicity of cobalt are not very prominent hence can take years to became visible in some people.

FATAL DOSE AND FATAL PERIOD

Intake of 250mg/Kg to 300mg/Kg will results in the symptoms of cobalt toxicity. More than 300mg/Kg of body weight will lead to severe poisoning within few weeks of intake. [6]

Table 1: LD_{50} of few compounds of cobalt. [7]

Compound	LD_{50} (mg/kg)
Cobalt chloride	80
Cobalt oxide	202
Cobalt chloride hexahydrate	786
Cobalt metal	6171
Cobalt sulphide	>5000

NORMAL/ REFERENCE VALUES

In normal unexposed individuals the range of cobalt concentration lies between 0.08µg/L to 0.50µg/L in blood and 60µg/L in urine. More than 5µg/L can cause toxicity. [6 7]

Table 2: Normal/ Reference and Toxic levels of Cobalt

Matrixes	Normal Level	Toxic Level
Blood	0.08 µg/L to 0.50 µg/L	5 µg/L
Serum	0.3 µg/L to 0.7 µg/L	1- 5.1 µg/L
Urine	60 µg/L	>60 µg/L

SYSTEMIC EFFECTS ON THE BODY

Various effects are visible in case of cobalt poisoning which includes cardiovascular effects, neurological, haematological, immunological, dermatological, ophthalmological, gastrointestinal and reproductive system dysfunction.

1. Cardiovascular

Cobalt sulphate is used as stabilizer in beer which can cause beer drinkers cardiomyopathy if taken for years with an average intake of 0.04 mgCo/kg/day to 0.1404 mgCo/kg/day. Cobalt Cardiomyopathy occurs due to the accumulation of cobalt in the heart tissues. This accumulation causes carotid body chemoreceptors to mimic the action of hypoxia. Initial sign of this disease includes GI effects which later resulted in cardiac problems. Other than this it causes failure of left ventricle, enlarged heart, pericardial effusion, cardiogenic shock, pathological changes in myocardium which include swollen fibres of muscle and proliferative interstitial tissue. [2]

2. Haematological effects

These effects occur because of the cease of heme production in vivo, since cobalt act upon minimum two different sites in biosynthetic pathway. Instead of heme cobalt protoporphyrin is formed. Cobalt induce heme oxygenase which might cause oxidation of heme in various organs and also act on heme-containing protein which may stimulate increase in EPO (Erythropoietin). [2]

3. Neurological

Accumulation of cobalt will lead to the formation of free radicals which results into neurodegeneration. Longer exposure will lead to the structural changes in the visual cortex [8]. It also leads to memory impairment, seizures, vertigo and altered mental status.[2]

4. Hepatic effects

Cobalt levels more than and equal to 0.014 mg/kg/day will result into problems in liver. These includes increased serum Bilirubin, central hepatic necrosis, increase in the levels of creatinine phosphokinase, Aspartate transaminase, Lactate dehydrogenase, Alanine transaminase, isocratic dehydrogenase, aldolase and ornithine carbamyl transferase. [9- 10]

CHEMICAL TESTS FOR COBALT POISONING

Qualitative Analysis

The biological samples which are analysed for cobalt poisoning includes urine, blood, serum and tissues. Detection of cobalt is quite easy to differentiate from others since its compounds produce different colour products. It cannot be confirmed from one single reaction since different metal salts can also give same outcomes.

- Cobalt test
  1. Cobalt test reagent is prepared by mixing 0.1% (wgt/wgt) of oxalic acid, 5.0% (wgt/wgt) of sodium acetate and 0.02% (wgt/wgt) of disodium-1-nitroso-2-napthol-3,6-disulfonate (nitroso R salt) in deionized water.
  2. To detect the presence of cobalt, 10 µl of sample solution is taken in a test tube and 50 µl of cobalt test reagent is added to it.
  3. A change in colour from yellow to bright red is observed.

4. This test gives positive result if cobalt ion concentration is above 8ppm. [11]

Quantitative Analysis

1. UV Visible Spectroscopy

   Cobalt has the ability to form complex with organic compounds which absorb light at specific wavelength. The absorbance in visible spectrum directly affects the colour perceived by the chemical in order to determine the metal.

2. X- Ray fluorescence (XRF)
   i. X- Ray fluorescence, a non-destructive method relies on bombarding a small part of part of sample with high energy x- ray photons which results in the ionization of the inner electrons of atoms.
   ii. This unstable configuration will result in filling of inner orbital electron with the outer shell electron which emits the x- ray photon as the difference in the energies between two orbitals. [12]
3. Inductively Coupled Plasma Optical Emission Spectrometry (ICP- OES)
   i. Inductively Coupled Plasma Optical Emission Spectrometry relies on the spontaneous discharge of light with specific wavelength from ions and atoms already excited in plasma.
   ii. A photodetector is used to convert the wavelength into electrical signal.
   iii. The sample is injected into the central channel of plasma core which is at a temperature of approximately 10000 ^{0} C after its conversion into an aerosol.
   iv. A complete Atomization of sample occurs in argon plasma, which help in minimizing the interferences.
   v. The solution detection limit for cobalt is 5 µg/L and the limit for sample detection is 2.5 µg/g can be achieved.
   vi. 228.616 nm, 230.786 nm and 238.346 nm are the spectral lines of emission used for cobalt. [12]
4. High Resolution Sector- Field Inductively Coupled Mass Spectrophotometer (HR-ICP-MS)
   i. High Resolution Sector- Field Inductively Coupled Mass Spectrophotometer is used to measure the concentration of cobalt in a sample.
   ii. 0.02 µg/L is the detection limit for cobalt.
   iii. Firstly, the sample is treated with conc. HNO_3 for the digestion of proteins and lipids present in sample.
   iv. Then the sample is diluted with the water and internal standard yttrium 89.
   v. The final solution is then introduced into the instrument and compared with the aqueous standards.
   vi. The detection limit of the instrument is highly specific, that is three times the background noise of the sample. [13]

SYMPTOMS OF COBALT POISONING

Symptoms or clinical appearances depends on the type, time of exposure and amount of dose. The most threatening toxicity occurs due to breathing of high doses of cobalt, which generally occurs to people residing in industrial areas. It may lead to chronic lung problems like asthma, shortness of breath etc.

In case of acute poisoning

Stage1: Gastrointestinal effects

- Nausea
- Vomiting
- Diarrhoea

Stage 2: Systemic Effects

- Rashes on skin

- Allergic dermatitis
- Blood in faeces
- Heavy breathing

In case of chronic poisoning

- Cardiomyopathy: enlarged and floppy heart, difficulty in pumping blood.
- Deafness
- Thyroid problems
- Vision problems
- Ringing in ears
- Nerve problems

DIAGNOSTIC INVESTIGATION

The diagnosis relies upon the combination of both the clinical history of patient and the laboratory findings.

1. The specimens to be tested includes whole blood sample, serum or urine.
2. Mostly the serum value is reported for the exact concentration of Co ions since it reflects the extracellular fluid levels.
3. Whereas some reports suggest that the whole blood value is the exact match of systemic exposure.
4. In case of lung involvement X- rays and ECG is performed.
5. The lab test utilises ICP-MS detection method. [5, 14]

MANAGEMENT/TREATMENT

If someone has been exposed to cobalt the care and treatment should be initiated to avoid further irreversible damage to the patient. Criteria of management in Cobalt poisoning include.

1. Immediate Care

On exposure to cobalt, leave the area of exposure and get some fresh air. If cobalt come in contact with skin, then thoroughly wash the skin area with water.

2. 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 lifetime.

3. Criteria for toxicologist consultation

There is no consensus regarding the treatment of patients with systemic symptoms of cobalt toxicity, and clinical response to these treatments is documented. However, the main objective of cobalt toxicity is to eliminate exposure to cobalt and treat systemic symptoms supportively. The physician in case of systemic toxicity can consult the toxicologist or poison control centre for more details. [15]

4. Hospital Management

- It starts with complete and thorough examination of the patient which includes serum level of cobalt, hepatic function, whole blood test, and 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 cobalt poisoning haemodialysis is performed and antidote is given to reverse the effects.
- Toxicity due to metal-on-metal implants involves removal of that implant and replacement with the traditional one. [17]
- Chelation therapy is another technique which is used to treat cobalt poisoning. Metal ions form stable complexes with chelators. Chelators

which are used in cobalt poisoning includes $CaNa_2$ EDTA, dimercaptopropanesulfonic acid (DMPS), dimercaptosuccimer (DMSA), N-acetylcysteine (NAC) and $CaNa_3$ DTPA. While performing the therapy the concentration of cobalt increases in urine and after the therapy the concentration decreases in serum by 61% and in blood by 70%. The dosage for the therapy is:

$CaNa_2$ EDTA- 30 to 40 mg/kg for adults, given intravenously two times in a day for 5 days followed up for maximum of five days after 48 hours break.

Dimercaptopropanesulfonic acid (DMPS)- 300 mg once in a day and it is given orally. This dose is given in case of chronic poisoning and can be increased in case of severe cobalt toxicity [1].

CONCLUSION:

Toxicity of cobalt is caused due to the exposure of large amount of cobalt for longer time, so it is highly important to avoid direct contact with cobalt. After getting into bloodstream it affects the major body organs. And various tests are performed to detect its toxicity using blood, serum or urine. ICP-MS is the method of choice which confirms the poisoning caused by cobalt. After the diagnosis proper treatment should be given to the patients who include chelation therapy at the hospital.

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