

REVIEW ARTICLE

BISMUTH POISONING WITH ANALYTICAL ASPECTS AND ITS MANAGEMENT

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Received: 12 February, 2019/ Accepted: 5 March, 2019

ABSTRACT: Bismuth is a chemical element with the symbol Bi and atomic number 83. It is a pentavalent metal which chemically resembles Arsenic (As) and Antimony (Sb). Bismuth salts, especially colloidal bismuth subcitrate (CBS) and bismuth subsalicylate, are widely used to treat peptic ulcers, functional dyspepsia, and chronic gastritis. Bismuth and most of its compounds are less toxic in comparison to other heavy metals like lead, antimony, cadmium, etc. The main organs involved in bismuth poisoning are kidney, liver and bladder. Skin and respiratory irritation can also follow exposure to respective organs. Large concentration of bismuth is contained in kidney and is primarily excreted through this organ while lesser amounts of bismuth are excreted via saliva, milk and bile. Routes of exposure are skin/eye contact, inhalation and ingestion. The toxic results developed by this heavy metal are serious ulcerative stomatitis, vague feeling of bodily discomfort, nausea, vomiting, loss of appetite and weight, pain in legs, arms and joints, depression and sleeplessness, pyorrhea and exodermatitis. Management of the bismuth poisoning is done in the same line as any other heavy metals, with irrigation of the stomach (gastric lavage) and chelating agents.

KEYWORDS: Bismuth, Poisoning, Toxicity, Treatment, Management etc.

INTRODUCTION:

Bismuth is a high-density, silvery, pink-tinged metal. Bismuth metal is brittle and because of its brittleness, it is usually mixed with other metals to make it useful. Its alloys with tin or cadmium have low melting points and are used in fire detectors, electric fuses, solders and extinguishers. The term 'bismuth' comes from the German word 'Weisse

Masse' which means white mass and latin word Bisemutum. Bismuth occurs as the native metal and in ores such as bismuthinite and bismite. Its major commercial source is as a by-product of refining lead, copper, tin, silver and gold ores. Examples of bismuth products used in medicine include bismuth subsalicylate, colloidal bismuth subcitrate,

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ranitidine bismuth subcitrate, bismuth subcarbonate, bismuth subnitrate, and bismuth subgallate. Some preliminary evidence suggests that bismuth carbomer enemas may reduce pouchitis that may occur after colonic removal. Bismuth subgallate has been studied for controlling odor after an ileostomy which is a hole surgically constructed in the abdomen to eliminate waste and bismuth subnitrate has been used for treatment of dyspepsia and bismuth subnitrate has been used for treatment of *Helicobacter pylori* infection. The reported toxic effects caused by overdose of bismuth compounds include encephalopathy, nephropathy, osteoarthropathy, gingivostomatitis, and colitis. Bismuth poisoning mostly affects the kidney, liver, and bladder. Chronic exposure to high levels of bismuth salts result in encephalopathy, whereas acute toxicity manifests as nephrotoxicity.¹⁻⁶

SOURCES OF BISMUTH

Common sources of Bismuth are as follows:

- About 0.02 µg/litre Bi is present in Sea water.
- In natural water, concentrations of Bismuth are found to be very low, usually less than 0.2 µg/litre.
- Anthropogenic sources of bismuth include copper, lead, silver and gold smelting, waste water and sewage sludge.
- In elemental abundance Bismuth ranks 69th in the Earth's crust and is considered almost two times as abundant as gold.
- Pure bismuth can also be obtained by reducing the oxide with carbon or by roasting the sulfide in the presence of charcoal and metallic iron to remove the sulfur.
- The most common mineral ores are Bismuthinite (Bi₂S₃) and Bismite (α-Bi₂O₃).
- The Tasna mine in Bolivia has the largest bismuth deposits and one mine in China.

- These are the only mines that have produced bismuth from a bismuth ore.
- As production of bismuth is a byproduct of processing lead ores, world reserves of bismuth are usually based on bismuth content of lead ores.
 - In some nuclear reactors, Lead-Bismuth Eutectic (LBE) alloys which contain 44.5% lead and 55.5% bismuth are used as a coolant.
 - Bismuth has been used traditionally for stomach problems. Bismuth subgallate has been used for controlling odor after an ileostomy which is a surgical opening in the belly wall to allow waste to be removed.
 - It is used in the manufacture of cosmetics and pharmaceuticals, ceramic glazes, pearlescent pigments, permanent magnets and safety devices in fire detection and extinguishing systems.
 - Bismuth can also be used in the electronics industry and in the production of catalysers, steel, aluminium and fusible alloys.
 - Addition of bismuth subnitrate to other medications such as antibiotics, may improve the elimination of bacteria over the medications alone.
 - Bismuth has been established as a safe and well-tolerated treatment for *Helicobacter pylori* infections in adults and children.
 - Bismuth subnitrate reduces the acidity of the stomach, as well as increase the production of a substance which improves healing of ulcers.
 - Bismuth carbomer enemas have been used for chronic pouchitis (inflammation of a surgically constructed bowel pouch) and bismuth subgallate for tonsillectomy (removal of tonsil).
 - Bismuth subnitrate, ginseng, and tang-kuei ten may reduce kidney dysfunction

associated with cisplatin treatment, although conflicting results exist.

EXPOSURE OF BISMUTH

Domestic

Risk of exposure are consuming medications that contain bismuth and using of cosmetic products.

Environmental

Bismuth metal is not considered toxic and poses minimum threat to the environment. Generally bismuth compounds have very low solubility but they should be handled with care because there is only limited information on their effects and fate in the environment.

PHARMACOKINETICS OF BISMUTH⁷⁻¹⁰

Absorption

Only approximately 0.2% of orally administered bismuth is absorbed systematically from the gastrointestinal tract. Minimal absorption of bismuth occurs from bismuth-tin shot embedded in muscles of waterfowl. Gastrointestinal absorption is also relatively poor, with the total absorption of ingested bismuth being about 1%. Then the bismuth which is absorbed is transported in the blood bound to a plasma metallothionein and widely distributes throughout tissues.

Bismuth accumulates in kidney, bone (metaphysis), liver, spleen, heart and muscle. With a half-life of months to years, bismuth in bone is very slowly turned over. Protein-bound bismuth also concentrates in the placenta, and can cross the placenta into the amniotic fluid and the fetus. Bismuth is primarily excreted via kidney as this organ contains the highest concentrations of bismuth. However, lesser amounts of bismuth are excreted through saliva, milk and bile.

Distribution and Excretion

Bismuth is primarily excreted via kidney as this organ contains the highest concentrations of bismuth. However, lesser amounts of bismuth are

excreted through saliva, milk and bile. Their solubilities are low in the blood, and can be easily removed with urine, showed no carcinogenic, mutagenic or teratogenic effects in long-term tests on animals. Its biological half-life for whole body retention is about 5 days but it can remain in the kidney for years in patients treated with bismuth compounds.

Mechanism of action/ toxicity

Adverse health effects are observed when nephrotoxicity of bismuth has been reported after exposure to pharmaceuticals containing this element. In renal proximal tubule cells, bismuth forms intranuclear inclusion bodies which have been shown by X-ray microanalysis to contain bismuth *in situ*. It has also been shown to induce the synthesis of the metallothionein (metal-binding protein). It has been found that bismuth produce cell deaths by necrosis rather than apoptosis which is the most likely mechanism being bismuth interaction with the renal tubule cell membrane. However, altered regulation of a number of genes was also observed.

ONSET AND DURATION

The symptoms occur over 26 hours after exposure however in case of lower dose, symptoms may occur over 8 days. The poisoning can be acute or chronic and the metal may enter the body by ingestion, inhalation or absorption through the skin or mucous membranes. Large doses can cause fecal impaction. Bismuth toxicity typically presents sub-acutely with mental changes of memory loss, psychosis and depression with prominent background of ataxia, tremors, myoclonus and seizures.

FATAL DOSE AND FATAL PERIOD

The fatal dose of bismuth is considered to be 524mg orally every 0.1 to 1 hour upto a maximum of 8doses/day(4192mg/day). Probable oral lethal dose in humans is 0.5 -5g/kg. Intoxication occurs

from its use in medicine. The time to peak conc. is typically within one hour. The distribution half life is approximately 1 to 4 hours, and the elimination half life is 5 to 11 days. Urinary bismuth is detectable 3 months after the last dose.

NORMAL/ REFERENCE VALUES

In unexposed individuals the level of Bismuth in blood is usually less than 0.05µg/ml. In acute toxicity the level remains high whereas in case of urine the normal levels ranges from 0-20mmol/l and in toxicity the level ranges from 400mmol/l.

Table 1: Normal/ Reference and Toxic values of Bismuth.

Matrixes	Normal level	Toxic level
Blood	<0.05µg/ml	0.05-0.1µg/ml
Urine	0-20 mmol/l	400 mmol/l

SYSTEMIC EFFECTS ON BODY

Bismuth poisoning exists and mostly affects the kidney, liver and bladder, although the degree of such damage is usually mild. Skin and respiratory irritation can also follow exposure to respective organs. Injection of large doses into closed cavities and from extensive application to burns, may cause serious and sometimes fatal poisoning. It is considered that the administration of bismuth should be stopped when gingivitis appears otherwise serious ulceration stomatitis is likely to result. Other toxic results such as vague feeling of bodily discomfort, the presence of albumin or other protein substances in the urine, diarrhea, skin reactions and sometimes serious exodermitis may develop.

Poisoning of industrial bismuth has not been reported but much of what is known about bismuth toxicity has been derived from its therapeutic uses. The solubility of most bismuth salts is very low and they are poorly absorbed by inhalation/ingestion. The main organs involved in bismuth poisoning are kidney, liver and bladder. Skin and respiratory

irritation can also follow exposure to respective organs. The primary routes of exposure are through inhalation/ ingestion of dust and fumes. Mental changes, Nervousness, Blood changes, Lymphocytosis and Bone marrow depression are observed following prolonged inhalation of bismuth.

Acute

Skin/Eye contact: Skin/eye may cause local irritation but would not cause tissue damage. It is not absorbed through skin.

Inhalation: Inhalation may irritate the upper respiratory tract. Its symptoms include sneezing, coughing and shortness of breath. Intense exposure causes abdominal spasms, sleep disturbances, nausea, fatigue, headache, vomiting, weight loss, anemia, pain in legs, arms and joints.

Ingestion: Symptoms are similar to those occurred in inhalation like nausea, diarrhea, weakness, pyorrhea, swelling of the buccal membranes, ulcerative stomatitis, vomiting and increased salivation. Other health effects might also be expected to occur, like metallic taste in the mouth and constipation or bloody diarrhea.

Chronic

Prolonged overexposure to bismuth may cause chronic health effects. Signs of toxicity may include skin reactions, loss of appetite and weight, fatigue, disturbances in sleep and depression. A bluish or brownish discoloration of the gums may also occur in severe cases due to bismuth deposition in the gums. It may also cause damage to central nervous system, gastrointestinal disturbances and anemia.

CLINICAL APPEARANCES/ SYMPTOMS IN CASE OF BISMUTH POISONING

In case of Bismuth poisoning, clinical appearance/systems will depend on different forms of bismuth and doses taken, which has been discussed as

1. Bismuth may lower the blood sugar levels so the caution is advised in people with diabetes or hypoglycemia, and in those taking drugs, supplements or herbs that affect blood sugar. Blood glucose levels should be monitored by a qualified healthcare professional, including a pharmacist, and medication adjustment should be necessary.
2. Caution is advised in individuals, with respect to use of bismuth, by individuals who take agents, that bind to opiate receptors, antidiarrheal agents, certain classes of antibiotics, phenytoin, probenecid, sulfapyrazone, and salicylates.
3. Products of bismuth may cause abnormal spots on chest radiographs, anxiety, abnormal sensations in facial skin, bad taste in the mouth, abdominal cramping, alopecia (hair loss), a plastic anemia (low blood cell count), bleeding around the kidney, brain dysfunction, effects on glutathione, pruritus (itchy skin), kidney failure, liver toxicity, muscle spasms, pain, depression, dry mouth, diarrhea, dark stools, long-term gastritis, blackening of the tongue, constipation, confusion, headache, hallucinations, glandular atrophy, lymphoid particle formation, trembling, vomiting, nausea, tinnitus, body pain, brain dysfunction, intestinal metaplasia, and difficulty in speaking.
3. Then small piece of cleaned copper strip is added to it and heated in a water bath.
4. Now the presence of bismuth is indicated by a gray deposit on the copper strip.
5. The pieces of dried shining copper strip are slowly heated in a Reinsch's tube after necessary cleaning.
6. Non-sublimation of copper strip on heating in Reinsch's tube is indicative of the presence of bismuth.

b. Potassium Iodide-Cinchonine Test

1. In a spotted tile, a portion of stained copper strip from the Reinsch's test is taken.
2. To dissolve the deposit, a few drops of Nitric acid are added.
3. The solution is then evaporated and the residue is divided into two portions.
4. One drop of potassium iodide solution is added to one portion, followed by a drop of acidified aqueous cinchonine solution.
5. Appearance of orange color is indicative of the presence of bismuth.

Quantitative Analysis

a. UV-Visible Spectroscopy method

Bismuth can be detected quantitatively by using UV-Visible spectrophotometry. Bismuth can form complexed with organic compounds which will give absorbance at specified wavelength.

b. Atomic Absorption Spectrophotometry method (AAS)

Atomic absorption spectrophotometry is good technique for the determination of Bismuth in biological materials using cold VGA technique. The absorbance of the standard solutions is plotted against the concentration of Bismuth. The

CHEMICAL TEST FOR BISMUTH POISONING

Qualitative Analysis

a. Reinsch's Test

1. In a China crucible, 5 ml of test solution is taken.
2. To it, few HCl drops are added.

concentration of Bismuth is obtained from the calibration curve.

c. Ion Chromatography

Ion chromatography is another important tool for the quantitative estimation of Bismuth in biological materials such as blood, urine, tissue, hair, nail etc.

d. Voltammetry/ Polarography method

Voltammetry/Polarography is another tool for quantitative analysis of Bismuth in biological materials.

e. ICP-OES/ICP- MS Method

Inductively Coupled Plasma Optical Emission Spectroscopy/ (ICE-OES) is an analytical technique that uses the emission spectra to quantify the Bismuth. It is a screening technique in acute poisoning. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) is latest advance technique for determination of heavy metals in microgram and nanogram and picogram levels. This is the instrument by which multiple elements can be determined simultaneously.

f. Neutron Activation and Analysis (NAA)

It is sensitive method for analysis of Bismuth and can be used to measure several elements simultaneously. In this technique sample is bombarded with the beam of neutrons which generate a range of radio isotopes and as these radioisotopes decay and emit radiation which can be measured, which is characteristic for a particular element.

MANAGEMENT/ TREATMENT OF BISMUTH POISONING

Without a clear history of exposure of bismuth it is very difficult to make diagnosis of bismuth toxicity. Systemic manifestation like renal failure

may not be recognizable for several days even after large overdose of bismuth. In these patients it is necessary to monitor renal and liver function for several days and treat failure conventionally.

General guidelines for management of bismuth poisoning are as follows:

Criteria for admission in bismuth poisoning

- A. **Observation at home:** Ingestion of single and small amount of bismuth are unlikely to cause systemic toxicity. Patient may be observed at home in asymptomatic condition.
- B. **Observation in hospital:** Ingestion of acute overdose or large amount of bismuth should be evaluated in hospital. Patient with symptoms of acute or chronic intoxication should be referred to health care facility.
- C. **Criteria for admission in hospital:** The patient with persistent vomiting or evidence of systemic toxicity should be admitted in hospital for supportive measures.
- D. **Criteria for toxicologist consultation:** If any patient develops systemic toxicity of bismuth then patient should consult a medical toxicologist or nearby poison control center.

Decontamination

Prehospital: No pre-hospital decontamination is needed.

Hospital: Gastrointestinal decontamination is generally not needed.

Mild toxicity

- a. Require symptomatic treatment
- b. Treat nausea and vomiting with antiemetics and fluids.

Severe toxicity

After acute ingestion, Gastric lavage should be considered only if the patient presents within one hour. Mechanical ventilation and sedation may be required for severe agitation and myoclonus. Chronic toxicity may generate Seizures and Encephalopathy. IV benzodiazepines are

required for the treatment of Seizures. **Diazepam:** In adults, 5-10 mg, repeat it in every 10-15 minutes as needed. In children, 0.2-0.5 mg/kg, repeat it in every 5 minutes as needed, or **Lorazepam:** In adults, 2-4 mg and in children 0.05-0.1 mg/kg.

Chelation Therapy

For severe acute and chronic poisoning, chelation therapy with BAL is often recommended. Chelation therapy with DMPS, DMSA, dimercaprol or d-penicillamine may be indicated in severe cases, but only after discussion with a medical professional.

Enhanced Elimination

There is no evidence of enhanced elimination by diuresis (increased or excessive production of urine) or hemodialysis (medical procedure to remove fluid and waste products from the blood and to correct electrolyte imbalances). Several case reports suggests that chelation with unithiol in combination with hemodialysis may increase bismuth elimination from body.

DISCUSSION AND CONCLUSION^{11-15:}

Consumption and production of bismuth compounds are increasing but a little information on the toxic effect and also the effective method in removal of bismuth compounds are available. Bismuth finds its main applications in pharmaceuticals, sprinkler systems, atomic fire alarms, solders, other alloys and even as a catalyst in rubber production. It is also used as pigments for cosmetics, glass and ceramics. Bismuth is a recognized toxic element and is not considered as carcinogenic. However, some of its compounds like Bismuth chloride need to be handled with care due to their corrosiveness. Over exposure to bismuth can lead to the formation of a black deposit on the gingiva. This is known as a bismuth line. Bismuth and its salts lead to kidney damage, although generally to a mild degree. However, large doses can be fatal, although industrially it is considered one of the less toxic heavy metals. Inhalation of bismuth may affect both the liver and kidneys.

Direct contact with bismuth may cause irritation to the eyes and skin. The main organs involved in bismuth poisoning are kidney, liver and bladder. Skin and respiratory irritation can also follow exposure to respective organs. Large concentration of bismuth is contained in kidney and is primarily excreted through this organ while lesser amounts of bismuth are excreted via saliva, milk and bile. Heavy metal poisoning is caused by the accumulation of certain metals like bismuth in the body due to exposure through industrial chemicals inhalation and ingestion. Treatment of heavy metal poisoning includes chelating agents such as Chemet which bind to the metal and are then excreted in your urine, diuretic called mannitol, hemodialysis and other special treatments if kidney failure occurs. The following steps are required for the prevention of Bismuth metal poisoning:

1. Wear masks and protective clothing if working around Bismuth and its compounds.
2. Since many metals accumulate in dust and dirt, keep these out of home as much as possible.
3. Check for any Bismuth metals listed on the labels of products brought to the home.
4. Use of bismuth products should be avoided by the individuals having blood disorders, hearing problems, gastrointestinal bleeding, peptic ulcer disease, sensitivity to salicylate, or tinnitus "ringing" in the ears.
5. Use of bismuth products may increase the
6. risk of bleeding so caution is advised in people with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.
7. Use of bismuth subsalicylate during breastfeeding must be avoided, as it may get absorbed by the infant.

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Cite of article: Jaiswal AK, Solanki S, Priya A, Sehrawat S, Kumar R, Kumar R. Bismuth poisoning with analytical aspects and its management. *Int J Med Lab Res.* 2019;4(1):47-54. <http://doi.org/10.35503/IJMLR.2019.0408>

CONFLICT OF INTEREST: Authors declared no conflict of interest

SOURCE OF FINANCIAL SUPPORT: Nil

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