Research Journal of Recent Sciences _____ ISSN 2277-2502
Vol. **2 (ISC-2012),** 58-67 **(2013)** *Res.J.Recent.Sci.*

Review Paper

Copper Toxicity: A Comprehensive Study

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Available online at: www.isca.in
Received 29th November 2012, revised 25th December 2012, accepted 15th February 2013

Abstract

Copper (Cu) is an essential trace minerals that is vitally important for physical and mental health. But due to wide spread occurrence of copper in our food, hot water pipe, nutritional deficiencies tablet and birth control pills increases chances of copper toxicity. Copper is not poisonous in its metallic state but some of its salts are poisonous. Copper is a powerful inhibitor of enzymes. It is needed by the body for a number of functions, predominantly as a cofactor for a number of enzymes such as ceruloplasmin, cytochrome oxidase, dopamine β-hydroxylase, superoxide dismutase and tyrosinase. It is present in several haematinics and its salts are also used therapeutically because of their astringent and antiseptic properties but sometimes copper salts are poisonous for human organ system.Copper Toxicity is increasingly becoming common these days. It is a condition in which a increase in the copper retention in the kidney occurs. Copper first start depositing in the liver and disrupts the liver's ability to detoxify elevated copper level in the body thus adversely affect nervous system, reproductive system, adrenal function, connective tissue, learning ability of new born baby, etc. When acidic foods are cooked in unlined copper cookware or in lined cookware where the lining has worn through, toxic amounts of copper can leech into the foods being cooked. This effect is exacerbated if the copper has corroded, creating reactive salts. The compounds of copper, often acting poisonously are blue vitriol (bluestone), the sulphate; and verdigris. In large amount taken at once, either of these will cause severe vomiting, pain in the abdomen, and purging; afterwards headache, and, in fatal cases, convulsions or paralysis before death. Slow poisoning will result from taking small amounts of copper daily, as in cooked or pickled articles, for a length of time.The current paper provides an overview of copper toxicity: acute and chronic, general symptoms, mode of administration medico-legal and forensic aspects, possible detection methods, treatment, etc.

Keywords: copper poisoning, chronic poisoning, heavy metal toxicity, copper sulphate.

Introduction

Copper (Tamba) is not poisonous in its metallic state but some of its salts are poisonous, especially the most common salts of copper are the Sulphate or the blue vitriol (Nila Tutia) and the sub-acetate or Verdigris (Zangal). Copper Sulphate is a crystalline salt with blue colour and metallic taste in a small dose of 0.5 g it acts as an emetic but in large doses, as an irritant poison produces gastric and intestinal irritation. Copper sub-acetate is a blue green salt formed by the action of vegetable acids on copper cooking vessels which are not properly lined and which have been used for cooking and storage for a long time. Copper compounds of Arsenic include Scheele's green (Copper Arsenite), Paris green or emerald green (Copper Aceto-arsenite) etc. and go by the name Hirwa in the local language .Copper is a powerful inhibitor of enzymes. Poisoning effect of copper will commence within 15-30 minutes.

Copper is a reddish brown nonferrous mineral which has been used for thousands of years by many cultures[1]. The name for the metal comes from *Kyprios*, the Ancient Greek name for Cyprus, an island which had highly productive copper mines in the Ancient world. Its atomic number is 29, placing it among the transition metals. The metal is highly conductive of both electricity and heat, and many of its uses take advantage of this quality. Copper can be found in numerous electronics and in wiring. It is also used to make cooking pots. This metal is also relatively corrosion resistant. For this reason, it's often mixed with other metals to form alloys such as bronze and brass. The metal is closely related with silver and gold, with many properties being shared among these metals. Modern life has a number of applications for copper, ranging from coins to pigments, and demand for the metal remains high, especially in industrialized nations. Many consumers interact with it in various forms on a daily basis.

In addition to being useful in manufacturing, copper is also a vital dietary nutrient, although only small amounts of the metal are needed for well-being. It appears in several enzymes, facilitates the absorption of iron, and helps to transmit electrical signals in the body. In high doses, however, the metal can be extremely toxic[2]. Copper can also saturate the water and soil, posing risks to wildlife. On a more benign level, it can stain clothing and flesh, as many people have probably noticed.

The circulation and proper utilization of copper in the body requires good functioning of the liver, gall bladder and adrenal glands. If any of those organs are impaired, the body cannot properly excrete and utilize copper. Initially, the copper will build up in the liver, further impairing its ability to excrete copper[3]. As copper retention increases, it will build up in the brain, the joints and the lungs, adversely affecting the structure and function of the tissues. Copper is a powerful oxidant causing inflammation and free radical damage to the tissues. To avoid these toxic effects, it must be bound to the binding proteins, ceruloplasmin and metallo-thionein. These proteins can become deficient due to impaired adrenal and liver function which allows free copper to build up[4]. It can have a toxic effect (similar to other heavy metals) on the body and mind and it is a contributor to many chronic illnesses and mental disturbances.

In a natural state, copper is rarely found pure. It is compounded with other elements, and the material must be treated before it can be sold. This can lead to serious environmental problems, especially when mining companies engage in unsound practices. The chemicals used to extract the metal can be toxic, as can the discarded elements and runoff associated with its purification. Many countries attempt to regulate their copper industries to prevent widespread pollution and the problems associated with it. Copper is a reddish brown nonferrous mineral which has been used for thousands of years by many cultures. The metal is closely related with silver and gold, with many properties being shared among these metals. Modern life has a number of applications for copper, ranging from coins to pigments, and demand for the metal remains high, especially in industrialized nations. Many consumers interact with it in various forms on a daily basis[5].

The incidence of copper sulphate poisoning varies at different geographical areas depending on the local use and the availability of other suicidal poisons. Its incidence is reported to be 34% and 65% of the total poisoning cases in two studies from Agra and New Delhi in 1960s. The mortality rates vary from 14-18.8%. In another study from Aligarh in 1970s, it was the commonest mode of poisonings at that center accounting to 118 cases over four and a half years. However, the incidence of copper sulphate poisoning is declining in certain parts of India. Chugh *et al.*, reported a decrease in the number of cases of acute renal failure attributed to intentional copper sulphate ingestion among patients admitted to a renal unit in northern India over a period of three decades from five per cent in the 1960s to one per cent in the 1980s. In another autopsy series from north India, copper sulphate ingestion was responsible for 22% of deaths due to poisoning from 1972 to 1977. However, it declined to 3.85 and 3.33% between 1977-1982 and 1982-1987 respectively. Pediatric cases of copper sulphate ingestion are rare, with only few case reports available in literature[6-8].

The main foods that have high amounts of Copper are: Shellfish, Nuts and Seeds (except for pumpkin seeds), Soybeans (tofu, miso, etc.), Legumes, Wheat, Coconut, Avocado, Chocolate, Coffee, Leafy Greens

Figure-1
Copper Sulphate

Figure-2
Copper Ornaments

Figure-3
Copper Rich Fruits

Figure-4
Worker In Copper Industry

Figure-5
Copper Coins

Figure-6
Copper Mines

History: For the history buffs, the first recorded use of copper occurred in agriculture in 1761 when it was discovered that soaking bean grains in a weak solution of copper sulfate prevented later plant damage through seed boring fungi. Since that time it has been used in a wide range of industries from pyrotechnics to viticulture (the science, production and study of grapes). In fact, there have been well-reported examples of chronic copper sulfate toxicity in vineyard workers. Repeated inhalation of copper sulfate mists (e.g. Bordeaux mixture) may induce a condition known as "vineyard sprayer's lung" and was first described in 1969 in Portuguese vineyard workers. Copper sulphate was among the first chemical substances used for fighting against plant diseases. Sulphate production in Russia started a little bit earlier, than in Europe, in 1725 at Lyalinskoe copper-smelting factory in the province of Perm. In Europe the first sulphate manufactory was founded only in 1769 in the French city of Rouen. It was believed that useful properties of copper sulphate as defender of plants were discovered by chance when Ireland was suffering from a famine caused by total devastation of potato crops by a potato disease (phytophthora). An observant reporter of a provincial newspaper noticed that potatoes on fields close to copper-smelting factories were not damaged by the disease whereas in other field turned rotten. Archaeological evidence suggests that copper is among the earliest metals used by humans. Numerous digs all over the

world indicate that it was used to make utensils, jewelry, and weapons. The metal is highly ductile, meaning that it can be easily worked and pulled into wire. For cultures which had minimal or crude metalworking abilities, it would have been easy to shape and work with. It is also easy to alloy, and many of the early metal alloys featured this metal**.** Bordeaux mixture- a product on the basis of copper sulphate for protection of plants, was discovered absolutely accidentally. French winemakers once addressed a request to chemist Joseph Louis Proust who at that time was already an honored scientist to prepare any remedy to deter thieves from stealing ripening grapes from plantations. Proust responded to the request with a suggestion to use for this purpose a mixture of copper sulphate water solution. A lot of time passed and in 1882 a French chemist Pierre Marie Alexis Millardet, passing by vineyards where Proust's mixture was very frequently used, observed that here there were no even traces of grape decay. Bordeaux mixture, or Bordeaux liquid (as it is called now) in a short time was spread worldwide and used to spray not only grapevines, but also potatoes, tomatoes, onions, apple-trees and pears.

General Symptoms: Metallic taste in mouth, salivation, burning pain stomach, nausea, vomiting, vomiting matter will be blue in colour, cramps of legs or spasm, colicky abdominal pain, diarrhea, urine is inky in appearance, severe headache and breathing may be difficult, jaundice, stool may be fluid and brown and bluish colour, allergies, Hair loss, anemia, anorexia, anxiety, attention deficit disorder, arthritis, asthma, autism, candida overgrowth, depression, dysmenorrhea, male infertility, prostatitis, fibromyalgia, migraine headaches, PMS, chronic infections, insomnia, cold perspiration indicates circulatory collapse, convulsion and coma precede death.

Pathology: Main brunt of copper toxicity is borne in the order by the erythrocytes, the liver and then the kidneys. Intravascular hemolysis appears 12-24 hour following ingestion of copper sulphate. Hemolytic anemia is caused either by direct red cell membrane damage or indirectly as a result of the inactivation of enzymes (including glutathione reductase) which protect against oxidative stress. Copper ions can oxidize hem iron to form methaemoglobin. This blood loses its oxygen carrying capacity. Clinically cyanosis and chocolate brown blood may be seen. Patients with cyanosis show at least 1/3 rd of the blood to be methaemoglobin.

Jaundice in copper sulphate poisoning is partly hepatic in origin in addition to hemolysis. Jaundice appears on the second or third day following ingestion. Liver damage has been attributed to liver mitochondrial dysfunction due to oxidized state. Nature of liver damage is both cell necrosis as well as obstruction. Obstructive factor is seen predominantly as opposed to toxic hepatitis. Level of bilirubin is directly proportional to the severity of the poisoning. Elevated levels of liver enzymes are seen in all except mild cases of poisoning. Liver biopsy reveals centrilobular necrosis, mononuclear infiltration and biliary stasis.

Intravascular hemolysis plays a major role in the pathogenesis of renal failure. The hem pigment released due to hemolysis and direct toxic effect of copper released from lysed red cells contributes to tubular epithelial damage of the kidney. Severe vomiting, diarrhea, lack of replacement of fluid and gastrointestinal bleed, leading to hypotension could also contribute to renal failure. Renal complications are usually seen on the third or the fourth day and onwards after the poisoning.

Copper sulphate being a corrosive acid, results in caustic burns of the esophagus, superficial and deep ulcers in the stomach and the small intestine. Changes of acute gastritis, hemorrhages in the intestinal mucosa, necrosis of the intestinal mucosa and perforation have been reported of eight kidney biopsies and tubules contained hemoglobin casts. Copper sulphate being a corrosive acid, results in caustic burns of the esophagus, superficial and deep ulcers in the stomach and the small intestine. Changes of acute gastritis, hemorrhages in the intestinal mucosa, necrosis of the intestinal mucosa and perforation have been reported.

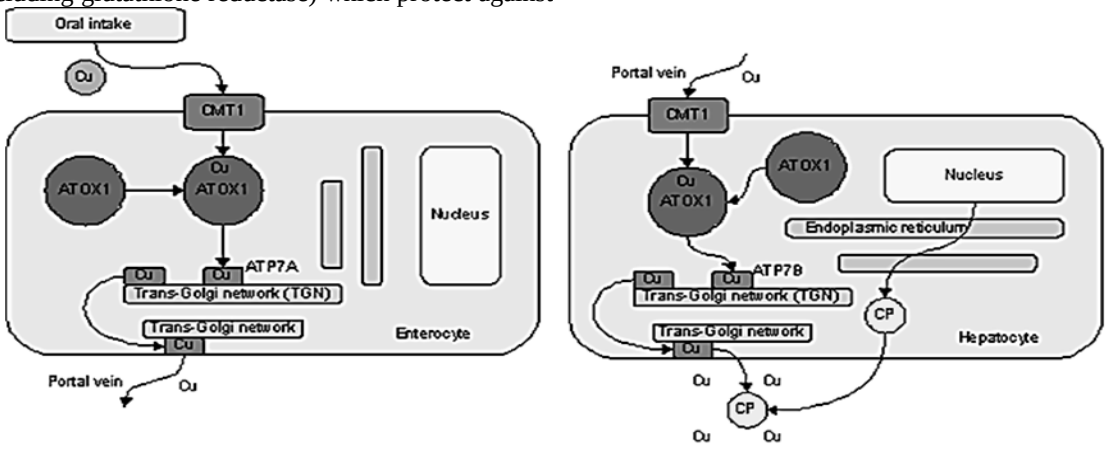

Figure-7
Pathology of Copper

Clinical Features: Gastrointestinal: The immediate symptoms following ingestion of copper sulphate universally is gastrointestinal in the form of nausea, vomiting and crampy abdominal pain. Vomiting usually occurs within 15 minutes of ingestion. Vomitus is characteristically greenish-blue. Hemorrhagic gastroenteritis associated with mucosal erosions, a metallic taste, burning epigastric sensation and diarrhea may occur. In severe cases hematemesis and malena occur. In a case series including 19 patients requiring hemodialysis after copper sulphate ingestion, 7(37%) developed gastrointestinal bleeding and in 5(26%) this was severe enough to cause significant hypotension.

Cardiovascular: In cases with severe poisoning cardiovascular collapse, hypotension and tachycardia can occur early within a few hours of poisoning and may be responsible for early fatalities or can occur late with other complications. Vomiting, diarrhea and GI blood loss are the factors usually responsible for hypovolemia. Severe methaemoglobinemia can result in cardiac dysrythmia and hypoxia which could contribute significantly to cardiovascular collapse. Other factors implicated are direct effect of copper on vascular and cardiac cells and sepsis due to transmucosal invasion. In a series of seven autopsies, five deaths occurred within an hour of admission due to shock. Four percent of patients in a series of 50 cases by Wahal et al had early cardiovascular collapse and succumbed within 10 hours of consumption of the poison.

Hematological*:* Intravascular hemolysis occurs 12-24h after ingestion. The discovery of significant methaemoglobinemia occurs early in the patient's clinical course and is rapidly followed by hemolysis. Coagulopathy can occur due to liver injury or direct effect of free copper ions on the coagulation cascade. The incidence of methaemoglobinemia ranged from 3.4% to 42% and intravascular hemolysis ranged from 47-65% in two case series.

Hepatic: Jaundice appears after 24-48h in more severe poisonings, which may be hemolytic or hepatocellular. It may be associated with tender hepatomegaly. Jaundice was seen in 11(58%) patients and 1(5%) patient died of hepatic encephalopathy in one series.

Renal: Renal complications are observed usually after 48h. Acute renal failure developed in 20-40% of patients with acute copper sulphate poisoning. Urinary abnormalities detected are oliguria, anuria, albuminuria, hemoglobinuria and hematuria.

Central *nervous system*: Central nervous system depression ranging from lethargy to coma or seizure is likely epiphenomenon related to other organ involvement.

Muscular: Rhabdomyolysis with high creatine phosphokinase (CPK) >3000IU have been reported. In one case myoglobinuria was detected on the second day and peak CPK level was observed on the sixth day.

Clinical features in paediatric patients: From the limited case reports available in paediatric patients, the clinical features in paediatric group resembles that of adults with early gastrointestinal feature and hemolysis usually occurring after 24h. Hepatic and renal toxicities develop one to two days after ingestion as in adult.

Copper Imbalances: It is possible for a person to become copper-toxic, copper-deficient or to have a condition called bio unavailable copper. The first two of these are fairly easy to understand brain and the reproductive organs. Copper may affect any organ or system of the body. However, it usually affects about four or five major systems of the body.

Symptoms of copper imbalance: Each mineral has "target organs" where it tends to build up. The places where copper accumulates are the liver first, then the brain and the reproductive organs. Copper may affect any organ or system of the body. However, it usually affects about four or five major systems of the body. These are the nervous system, the female and male reproductive system, connective tissues such as hair, skin and nails and organs like the liver. Let us discuss each of these in detail.

Copper and the Nervous System: Dr. Paul Eck called copper the "emotional mineral". The reason for this is that copper and imbalances related to it have such a profound impact on the central nervous system. The psychiatric implications of copper imbalance are tremendous, even if copper did not affect other body systems. We regularly work with every known psychological and psychiatric condition and most of these individuals improve when copper is balanced in the body. The overall effect of copper appears to be to enhance all emotional states in a human being. Dr. Eck felt that copper stimulates the diencephalons or old brain. Zinc is needed for the new brain or cortex. This brain associated with the "higher emotions" such as reasoning, compassion and love.

When an imbalance between these exists, the person tends to revert to the use of the old brain, also called the animal brain or emotional brain. This can lead to a tendency for every possible emotional condition affecting human beings. Nervous system dysfunctions involves different mental and emotional conditions ranging from moderate to suicidal depression and anxiety to violence, obsessive-compulsive disorder, bipolar disorder, phobias, Tourette's syndrome and schizophrenia. Others that respond amazingly well to balancing copper include epilepsy, ADD, ADHD, autism, delayed mental ,panic attacks, migraines, spaciness, brain fog, mind racing, insomnia, nervousness, irritability and others also often involve copper.

Copper and Infections: Copper imbalance is also very much related to all fungal infections especially sinus and other fungal infections, in particular. These often include common sinus conditions that give few symptoms such as a stuffy nose or post-nasal drip in millions of people. Copper is also involved in acute

and chronic candida albicans in the intestines and elsewhere. Copper is critical for aerobic metabolism, so copper imbalances allows fungal organisms to thrive in the body and must be corrected to reduce these infections, in most cases. This is why some people simply cannot get rid of candida albicans or chronic yeast, parasitic infections, sinus infections and others. Copper is also linked to many other types of infections because zinc is needed for the proper immune response.

Copper and the Reproductive System: Premenstrual syndrome: Women tend to have higher levels of copper than men. Women also have more symptoms related to copper imbalance. The symptoms of PMS mimic the symptoms of copper imbalance. This occurs because estrogen levels and copper levels correlate well and both increase before the menstrual period. For this reason, taking extra zinc and vitamin B6 before the menstrual period can often lower copper enough to reduce the symptoms of premenstrual tension for this reason. At times, however, the cause of PMS is more complex. Other symptoms related to the sexual organs include amenorrhea, dysmenorrheal, fibroid tumors, ovarian cysts, pelvic inflammatory disease, fibrocystic breast disease, endometriosis and possibly pelvic inflammatory disease.

Miscarriages and infertility: Copper is required to hold onto a pregnancy. Studies indicate that women with low estrogen and often low copper have more miscarriages. This is important for some women to know. Correcting the copper imbalance can help immensely with normal pregnancy. Infertility, on the other hand, is more common among women with elevated or bio unavailable copper. This may be due, in part, to weak adrenals that, in turn, give rise to copper imbalance. Fertility problems, however, can be due to many factors.

Low libido in women and men: This is also linked to copper imbalance. Since copper raises the hair and tissue calcium level, women, in particular, with very high copper levels or hidden copper on their hair analyses, often lose interest in sex. Their energy declines and the body can become a bit "numb" because excessive tissue calcium tends to render the nervous system less sensitive. Low sexual interest in men is also related to copper, which interferes with zinc metabolism in many instances. Men's sperm and fluids are very rich in zinc. If they become depleted, male fertility and male sexual performance will always suffer. Most of the time, these problems are easy to overcome by correcting the levels of zinc and copper in the body using nutritional balancing methods. Estrogen dominance and copper. Copper-toxic women are often estrogen dominant. This means they have more estrogen in their bodies, proportionately, than they have progesterone. However, we rarely use progesterone therapy. In fact, even natural or bio-identical progesterone therapy may be poorly tolerated in copper-toxic women and even men. It also tends to be a little toxic, so we avoid it if at all possible. Instead, if we balance the copper, the symptoms of estrogen dominance such as premenstrual tension, vanish quickly and completely. Bio unavailable copper and progesterone and body shape. Other women, usually those with bio unavailable copper are low in estrogen. Their bodies are often more linear in shape and less "curvy". Of course, copper is not the only factor affecting hormones. Some pesticides, for example, mimic the effects of estrogen and can affect the hormone balance.

Men and copper imbalance: Boys and men are far more affected when copper is out of balance than are women in many cases. Men should be zinc dominance. While most women have more copper in their bodies, men, by contrast, should be zinc-dominant. Zinc, a 'masculine' element, balances copper in the body and is essential for male reproductive activity. Among the boys, symptoms that are most prominent are growth and developmental delay, ADD, ADHD, autism and related brain disorders. Among men, symptoms of copper toxicity, usually, include prostate enlargement, prostate infections and to some degree prostate cancer. Others include ED or erectile dysfunction that used to be called impotence, depression, anxiety and even violence. Others are testicular pain and testicular cancer in some cases.

Secondary sex characteristics and copper includes sexuality that is more mental and emotional than they are physical. For example, some men just love sex and women, while others are less sexual. The differences have to do with hormone levels, and often with the copper imbalance. Homosexuality, for example, is often related to copper levels for this reason. This is true for women as well as for men. Birth control pills and copper IUDs (intra-uterine devices for birth control) . These two birth control methods definitely affect copper metabolism in the body. While some women can handle them, others experience depression, anxiety, personality shifts and many horrible side effects from them, either acute or chronic. This aspect of women's "sexual revolution" has probably caused more disasters in women's health than any other. Developing cancer, for example, can take years so women do not understand the dangers. Another curious effect of copper excess in women can be excessive sexual interest or sexual dysfunctions in women. This has something to do with the estrogen levels and liver toxicity due to the copper imbalance. Other sexual difficulties in both men and women such as pain on intercourse, vaginal dryness and others may have to do with copper imbalance as well.

Copper and Connective T**issue:** Copper is required for collagen formation. Copper deficiency is associated with osteoporosis and other cardiovascular conditions. Excess copper or bio unavailable copper often causes connective tissue problems, interfering with the disulfide bonds in connective tissue causes arthritis osteoporosis, stretch marks and joint problems of other kinds. Others include scoliosis, hypnosis (bad posture) and many of the conditions of the skin, hair and fingernails and toenails. Others are some diseases the muscles, ligaments and tendons and back problems due to muscle weakness.

Medicolegal Aspects: Copper occurs in some fungicides and in small medical doses in tablets with the sulphates of Iron and Magnesium. Copper Sulphate is used as an antidote in Phosphorus poisoning.

Acute fatal poisoning with copper is very rare. Copper as a metal is not poisonous and swallowed. Copper coins are not known to have produced poisoning. However all copper salts are poisonous. Copper sulphate has been taken in large doses for purposes of suicide. It is not adaptable to criminal administration owing to the colour and strong metallic taste possessed by its salts. Copper sulphate has been sometimes swallowed by children attracted by its colour.

Accidental poisoning has also occurred when copper has been added in order to keep the green colour of vegetables. Copper sulphate has been rarely used as a cattle poison. The formation of sub acetate on copper vessels is an alleged cause of poisoning resulting from contamination of food stored in such vessels. Prolonged use of water stored in copper vessels over a long period of time is also responsible for chronic copper poisoning. Also vegetables cooked and pickles stored in copper vessels induce a reaction leading to the formation of subacetates again leading to chronic poisoning.

Forensic Aspects: Acute Poisoning: The skin may be yellow owing to jaundice greenish blue froth may be coming out of the mouth and nostrils. The most striking appearance is the bluish or greenish colouration imparted to the gastric mucosa. The mucous membrane is congested and injected an occasionally shows eroded patches. The intestinal mucous membrane may share the same appearances.

These commence within 15-30 minutes. There is a metallic taste in the mouth with salivation and thirst, a sensation of burning with abdominal pain [colic], vomiting, diarrhea and collapse, the usual effects of any irritant poison. The vomited matter is coloured green or blue and must be distinguished from bile or bilious vomit. Addition of Ammonium Hydroxide turns the vomit deep blue while bile remains unchanged. The stools are liquid and brown/bluish and may even be bloody. The urine is inky in appearance, diminished in amount and contains albumin and casts. Uremia may occur in some cases. There may be severe headache and breathing may be difficult. Anaemia may be common. In severe cases, jaundice is common and there are spasms of the extremities. Cold perspiration indicates circulatory collapse. Convulsions and coma precede death. The patient is likely to recover if symptoms are mild after the first 6 hours.

The amount of copper sulfate that is lethal to one-half (50%) of experimental animals fed the material is referred to as its acute oral lethal dose fifty, or LD_{50}. The LD_{50} for copper sulfate is 30 mg/kg in rats. Ingestion by animals of three ounces of a 1% solution of copper sulfate will produce extreme inflammation of the gastrointestinal tract, with symptoms of abdominal pain, vomiting, and diarrhea. When copper sulfate is given intravenously, or injected into the vein, as little as 2 mg/kg copper sulfate is lethal to guinea pigs; and 4 mg/kg is lethal to rabbits.

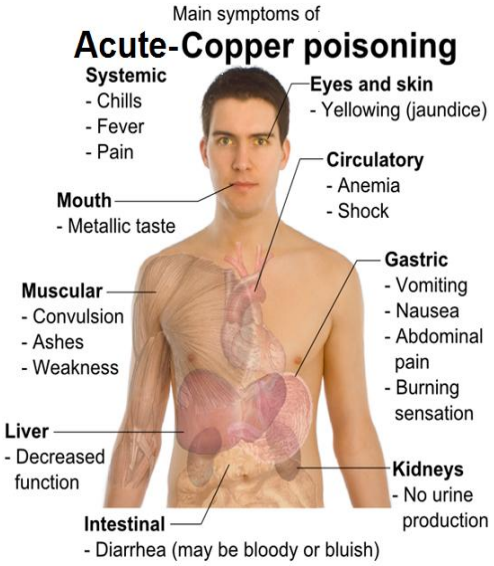

Figure-8
Acute Copper Poisoning

Chronic Poisoning: This may result among the workers who handle this metal or its salts. It may result from the continued use of copper vessels for preparing and preserving food and keep water whole night and consuming it tomorrow. Sometime person uses copper ornaments it reaches to body due to absorption through skin. The poison enters the system by absorption from the alimentary canal, by the lungs in the form of dust and partly by the skin in handling the metal or its salts.

In chronic poisoning the main signs and symptoms are allied to poisoning with lead. The usual symptoms consist of a metallic taste in the mouth; a green line on the gums at the base of the teeth; gastro-intestinal symptoms, such as nausea, vomiting, colic, diarrhea, constipation; and general signs of progressive emaciation, viz. anemia, malaise and debility.

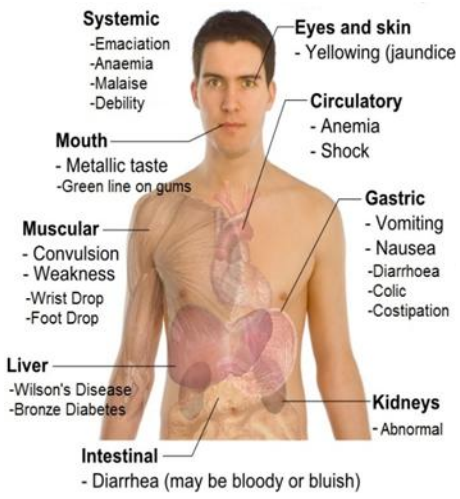

Figure-9
Chronic Copper Poisoning

Postmortem findings: Acute Poisoning: The skin may be

yellow owing to jaundice, greenish blue froth maybe coming out of the mouth and nostrils. The most striking appearance is the bluish or greenish colouration imparted to the gastric mucosa. The mucous membrane is congested and injected and occasionally shows eroded patches. The intestinal mucous membrane may share the same appearances.

Chronic Poisoning: The chief postmortem appearances consist of parenchymatous injury to the heart, liver and kidneys. Mallory has described haemo-chromatosis [bronze diabetes] from chronic copper absorption. Decreased hemoglobin and erythrocyte count is also a chief finding. Reddened gastric and alimentary canal walls are seen in most cases.

Detection: Method 1: Slowly place 0.1 ml of sample on a filter-paper to give a spot no greater than 1 cm in diameter, drying with a hair drier if necessary. Expose the spot to ammonia fumes from concentrated ammonium hydroxide in a fume cupboard, and add 0.1 ml of dithiooxamide solution to the spot. Copper salts give an olive-green stain. Chromium salts also give a green stain, which is normally visible before the dithiooxamide is added. A number of other metals give yellow-brown or red-brown colours with this reagent.

Method 2: Place 0.1 ml of sample in a well of a porcelain spotting tile and add 0.05 ml of dilute hydrochloric acid. Mix 0.1 ml of ammonium mercurithiocyanate reagent with 0.1 ml of zinc acetate solution and add to the sample in the well. A violet precipitate of zinc mercurithiocyanate forms in the presence of copper salts.

Method 3: Place 0.1 ml of sample in a well of a porcelain spotting tile and add 0.05 ml of dilute hydrochloric acid. Mix 0.1 ml of ammonium mercurithiocyanate reagent with 0.1 ml of zinc acetate solution and add to the sample in the well. A violet precipitate of zinc mercurithiocyanate forms in the presence of copper salts.

Analytical Techniques

Neutron Activation Analysis: Neutron activation analysis (NAA) is a nuclear process used for determining the concentrations of elements in a vast amount of materials. NAA allows discrete sampling of elements as it disregards the chemical form of a sample, and focuses solely on its nucleus. The method is based on neutron activation and therefore requires a source of neutrons. The sample is bombarded with neutrons, causing the elements to form radioactive isotopes. The radioactive emissions and radioactive decay paths for each element are well known

Atomic Absorption Spectroscopy: Atomic absorption spectroscopy is a powerful instrumental technique used for quantitative analysis of metal present in liquid. This method is very sensitive detect metals lower than 1ppm. Concentration and required no sample preparation and requires radiation source of metal which is under analysis There is one limitation that you can analyzed only one metal at one time.

In atomic spectroscopy, a different hallow cathode lamp is to be used for each element to be tested. It means that an element which is used in the construction of cathode lamp can be detected only. It is used to detect presence of copper in food material. It involves digestion of trace metal with dilute sulphuric acid or with nitric acid or with 50% of hydrogen peroxide it will shows the presence of copper in beers.

A flow injection on-line co precipitation system with diethyldithiocarbamate (DDTC) nickel (II) being used as a carrier was coupled to the flame atomic absorption spectrometry (FAAS) for the determination of trace copper, in environmental and biological samples. Metal ions were on-line co precipitated with DDTC-Ni (II) in 0.3 mol l^{-1} nitric acid and the precipitate was collected in a knotted reactor. The precipitate was then dissolved by isobutyl-methyl-ketone (IBMK), and the concentrated zone was transported directly into the nebulizer-burner system of a FAAS. Enhancement factors obtained for copper at the sampling frequency of 60 h^{-1}. The detection limit is 0.5 $\mu g \cdot l^{-1}$ for copper.

X-ray Diffraction: This method is based on the scattering of x-ray by crystal.

UV-Vis Spectroscopy: UV- Vis spectroscopy is used for qualitative and quantitative analysis of compounds It is used for determination of copper in sugar cane spirits. The copper reacts with biquinoline forming a pink complex with maximum absorption at 545 nm. The reaction occurs in the presence of hydroxylamine, ethanol and Triton X-100 tensioative. Determination of copper is possible in a linear range 0.2–20.0 mg L^{-1} with a detection limit 0.05 mg L^{-1}. The great advantages of the proposed methodology are the elimination of liquid–liquid extraction step and the use of toxic organic solvents, like dioxane, to dissolve the reagent.

Fluorescent Technique: Merocyanine dye allows copper to be detected using fluorescence spectroscopy.

Treatment Decreasing absorption: After acute ingestion of copper sulphate, in the pre hospital setup, immediate dilution with water or milk is advisable. The same action is extrapolated from recommendations for management of corrosive ingestions. In corrosive ingestion one should avoid emesis and should begin early dilutional therapy. Water may be used initially to dislodge adherent solid particles, as well as to dilute the caustic ingestion. It is important not to be excessively aggressive with dilution, as this may cause nausea, vomiting and possible aspiration.

Emesis should be avoided to prevent re-exposure of the esophagus to the corrosive agent. In copper sulphate poisoning vomiting is likely to occur spontaneously and hence patient may

require antiemetic therapy. In corrosive acid ingestion, there is a risk of perforation if blind gastric lavage is attempted, however in patients with large intentional ingestion of acid who presents within 30 min; consideration can be given to cautious placement of narrow naso-gastric tube suction to remove the remaining acid in the gut.

Activated charcoal administration should be considered after a potentially dangerous ingestion. A dose of oral activated charcoal, while of unproved benefit, is unlikely to be harmful and may have potential adsorptive capacity for copper. Usual dose is 25 to 100 gm in adults and adolescents and 25 to 50 gm in children aged 1 to 12 years (or 0.5 to 1 gram/kilogram body weight). Administer charcoal as aqueous slurry; most effective when administered within one hour of ingestion. Use a minimum of 240 ml of water per 30 gm charcoal.

Supportive measures: **Management of corrosive burns**: If corrosive oesophageal or gastric damage is suspected upper GI endoscopy should be carried out, ideally within 12-24 h, to gauge the severity of injury. This recommendation is extrapolated from experience with ingestion of acids and /or alkaline corrosives.

Endoscopic procedures done during the early period after corrosive ingestion has shown to be relatively safe without any complications. In a series of 94 patients with corrosive ingestion, GI endoscopy was performed in 81 patients within 24h and in 12 patients within 48h. The procedure was not associated with any complications. Similarly, in another series of 16 patients with corrosive acid ingestion, fiber optic endoscopy was done in 13 patients within 24h. The authors concluded that endoscopy did not give rise to any complications and it helped in grading the injury caused by corrosive acids, planning the management of patients and also in predicting the prognosis. The period of wound softening starts on the second or third day post-injury and last for roughly two weeks during which time there is an increased risk of perforation if endoscopy is performed. An early surgical opinion should be sought if there is any suspicion of pending gastrointestinal perforation or where endoscopy reveals evidence of grade III burns.

Sucralfate may help to relieve the symptoms of mucosal injury. Adequate human data regarding role of steroid in caustic burn is yet to be generated. The most suitable group to receive corticosteroid (with antibiotic) is probably the patients with grade IIb injuries (submucosal lesions, ulcerations and exudates with near circumferential injuries). In patients with grade III ulcers (deep ulcers and necrosis into periesophageal tissues) stricture formation occurs, irrespective of steroid administration. Moreover, steroids may mask or worsen the complications of corrosives in grade III patients and hence steroids are contraindicated.

Considering the experience with the use of steroid in copper sulphate poisoning, in a study of copper sulphate poisoning by Gupta et al., the mortality was lower in a group of 26 patients treated with steroids as compared to those without steroids. However, this was not a randomized-controlled study. The role of steroid has not been tested in any other controlled studies to strongly recommend this therapeutic intervention.

Methaemoglobinemia: Patients with symptomatic methaemoglobinemia should be treated with methylene blue. This usually occurs at methemoglobin levels above 20 to 30 percent, but may occur at lower methemoglobin levels in patients with anemia or underlying pulmonary or cardiovascular disorders. Administer oxygen while preparing for methylene blue therapy.

Methylene blue enhances the conversion of methemoglobin to hemoglobin by increasing the activity of the enzyme methemoglobin reductase. Initial dose is 1-2 mg/kg/dose (0.1 to 0.2 ml/kg of 1% solution) intravenously over 5 minutes. The dose may be repeated if cyanosis does not disappear within one hour. At high levels of methemoglobin (>70%), methylene blue reduces the half life from an average of 15-20 hours to 40-90 min. Hence, improvement from methylene blue therapy should be observed within one hour of administration.

Failure of methylene blue therapy suggests inadequate dose of methylene blue, inadequate decontamination, G-6-PD deficiency, NADPH dependent methemoglobin reductase deficiency. Further, methylene blue action requires intact erythrocytes and hence if hemolysis is severe, it may be ineffective in copper sulphate poisoning. Large doses of methylene blue itself may cause methaemoglobinemia or hemolysis and the same needs to be considered while administering this agent. It is contraindicated in G-6-PD deficient patients in whom it may cause hemolysis. Exchange transfusion and/or the transfusion of packed red blood cells may be useful for methylene blue failures or for patients with G6PD or NADPH methaemoglobin reductase deficiency. (Nitrates, Nitrites and methaemoglobinemia. Hyperbaric oxygen may be beneficial if methylene blue is ineffective. Hyperbaric oxygen increases the dissolved oxygen which can protect the patient while the body reduces methaemoglobin. Another alternative to methylene blue is the reducing agent ascorbic acid which can be administered 100-500 mg twice daily either orally or intravenously. But, this agent probably has a minor effect on increasing methemoglobin reduction and the clinical experience with the use of this agent is limited.

Hypotensive episode: Hypotensive episode should be treated with fluids, dopamine and noradrenaline.

Rhabdomyolysis: Early judicious fluid replacement of 4-6 L/day with careful monitoring for fluid overload, mannitol (100 mg/day) and urine alkalinization are suggested early in the course, but definite evidence for the efficacy of these measures is lacking.

Chelation therapy: There is little clinical experience with the use of chelators for acute copper sulphate intoxication. Data on efficacy is derived from patients with chronic copper intoxication (Wilson's disease, Indian childhood cirrhosis) and experimental animal studies. British anti Lewisite (BAL), D-Penicillamine, 2, 3-dimercapto-1-propane sulfonate, Na+ (DMPS) and ethylene diamine tetra acetate (EDTA) have been used. In severely poisoned patients the presence of acute renal failure often limits the potential for antidotes.

Penicillamine: D-Penicillamine has been used to treat acute copper intoxication, but data regarding efficacy are lacking. Adult dose: 1000 to 1500 mg/day divided every six to 12 h, before meals. Pediatric dose: Initially 10 mg/kg/day gradually increases to 30 mg/kg/day divided in two or three doses as tolerated. Doses up to 100 mg/kg/day in four divided doses; maximum one gram/day may be used depending on the severity of poisoning and adverse effects. Avoid in patients with penicillin allergy. Proteinuria, hematuria, renal failure, bone marrow suppression and hepatotoxicity are the common adverse effects.

Dimercaprol/BAL: Intramuscular BAL is probably appropriate in patients in whom vomiting and gastrointestinal injury prevents oral D-Penicillamine administration. BAL- copper complex primarily undergoes biliary elimination and hence it is useful in patients with renal failure. However, BAL may be less effective than D-Penicillamine and hence, when tolerated, D-Penicillamine therapy should be started simultaneously or shortly after the initiation of therapy with BAL. Dose: 3 to 5 mg/kg/dose deep intramuscularly every four hours for two days, every four to six hours for an additional two days, then every four to 12 h for up to seven additional days. Adverse reactions are urticaria and persistent hyperpyrexia.

Edetate calcium disodium: The dose of this agent is 75 mg/kg/day deep intramuscularly or slow intravenous infusion given in three to six divided doses for up to five days; may be repeated for a second course after a minimum of two days; each course should not exceed a total of 500 mg/kg. Complications include renal tubular necrosis.

Enhanced Elimination: Hemodialysis to remove copper is ineffective, but may be indicated in patients with renal failure secondary to copper poisoning. Peritoneal dialysis with salt-poor albumin resulted in extraction of more copper than dialysate without albumin. However, the amount of copper removed by peritoneal dialysis was very small. There is insufficient evidence regarding any role of hemoperfusion and hemodia filtration for copper elimination.

Case Studies: Case Study 1: A frantic father called the Illinois Poison Center after his 3 year-old daughter inadvertently ingested copper sulfate. During the case review, it was discovered that the father was using the product as an algaecide to clean their outdoor pool. Unfortunately, he placed this liquid in an unmarked clear plastic bottle which to his unsuspecting daughter looked like a refreshing summer drink. She consumed it and developed symptoms of GIT irritation and vomiting. She was immediately taken to the hospital where she was observed overnight and fortunately discharged the following day feeling much better.

Case Study 2: In India, a case was reported where a woman was admitted to the hospital with severe vomiting of bluish green colour. It was suspected a case of Copper Sulphate poisoning. Addition of Ammonium Hydroxide to confirm the bilious nature of the vomit turned out negative and on enquiry it was revealed that she was pregnant and it was finally found to be a case of unusual termination of pregnancy using "Nila Tutia", Copper Sulphate given by a Quack. Luckily, the woman survived. A case was registered against both the woman and the Quack.

Case Study 3: Two hundred seventy-five United States coins were discovered in the stomach of a mentally disturbed individual at autopsy. Many coins containing copper were corroded by prolonged contact with gastric juice, with subsequent absorption and deposition of copper in the liver and kidneys. The patient died from complications related to the acute toxic phase of chronic copper poisoning. As a discussion to the case, foreign-body ingestion, gastric bezoars and the mechanism of copper toxicity is presented. To our knowledge, this is the first death due to copper intoxication following a massive ingestion of coins.

Case Study 4: Gwalior, India: Copper sulphate was used as fungicide in a field and the excess was stored in the store room. A worker in the field had a word fight with the owner of the filed over wage-issues, following which he ingested the copper Sulphate stored in the store room in a attempt to commit suicide. But he was rushed to the hospital in time. His signs and symptoms were monitored and treatment was given. He survived.

Conclusion

Copper in a metallic form is not poisonous but some of their salts such as sulphates of copper and sub-acetate of copper are poisonous nature. Copper in small doses act as an emetic but larger dose causes gastrointestinal irritation**.** Copper is found in certain foods in greater quantity such as meats, eggs, poultry, nuts, seeds and grains, but certain foods are quite low in copper content such as fruits vegetables some nuts and grains. Those who are fast oxidizers require a lot more copper. Slow oxidizers often have excessive copper in their bodies. Thus they are far more prone to copper imbalance of this nature. Without sufficient binding proteins, unbound copper may circulate freely in the body, where it may accumulate primarily in the liver, brain and female organs. This may result among the workers who handle this metal or its salts. Chronic poisoning occurs due

to continuous use of copper vessels for preparing and preserving food and prolonged use of water stored in copper vessels over a long period of time is also responsible for chronic copper poisoning. The poison enters the system b absorption from the alimentary canal, by the lungs in the form of dust and partly by the skin in handling the metal or its salts. The places where copper accumulates are the liver first, then nervous system, the female and male reproductive system, connective tissues such as hair, skin and nails. Copper metallic poisoning depends upon the mode of administration, if copper is swallowed as a metallic form is not poisonous but if taken as a vaporized form it ac as a poison. The formation of sub acetate on copper vessel, contamination of food stored in such vessels and prolonged use of water stored in copper vessels over a long period of time must be checked to control chronic copper poisoning.

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