CYANIDE POISONING IN ANIMALS

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ABSTRACT

Cyanide exists in nature as well as it is also released in environment due to anthropogenic activities. Being a potent inorganic poison, it has significance in veterinary clinical and animal husbandry management practices. The incidences of cyanide poisoning are not uncommon and often results in high mortality of economically precious dairy animals. The major fodder crops ‘sorghum’ is associated with incidences of cyanide toxicity in majority of cases. Most of livestock species including cattle, buffaloes, sheep and goats are susceptible and affected. Animals exposed to cyanide through fodder show symptoms of hypoxia, respiratory distress, bluish discoloration and neurological signs and symptoms. Prompt treatment with specific antidote, if not employed leads to death. The implementation of preventive and controlling strategy is only way to overcome this loses. The present review comprehensively outlines the detailed aspects of cyanide toxicity in domestic animals covering recent advancement in toxicodynamics and pharmaco-therapeutics of its treatment.

KEY WORDS: Cyanide, anthropogenic, toxicodynamics, pharmaco-therapeutics

INTRODUCTION

The term cyanide refers to any compound that contains the cyanide ion (CN⁻), consisting of a carbon atom triple bonded to a nitrogen atom (EPA, 2010). Cyanide originates primarily from anthropogenic sources in the environment, but cyanide is also released from biomass burning, volcanoes, and natural biogenic processes from higher plants, bacteria, and fungi (ATSDR, 2006). Among different inorganic poisoning studied till to date, cyanide is one of the most potent inorganic poison of mammals. First publication about cyanide poisoning was by Wepfer in 1679 A.D., which describes effect of bitter almond extract and in 1782 A.D., Swedish chemist Scheele identified and isolated cyanide from cherry laurel (Sykes, 1981 and Borowitz et al., 1992). Cyanide exists in two from, free HCN and bound from. The bound form is cyanogenic glycoside, which is widely distributed in nature among 100 families of flowering plants. They are also found in some species of ferns, fungi and bacteria (Harborne, 1972 and 1993). Many plants have ability to synthesize cyanogenic glycosides by a process known as Cyanogenesis. These cyanogenic glycosides, upon enzymatic hydrolysis, release...
cyanohydrin acid (HCN) (Harborne, 1972, 1986 and 1993).

**Synonyms**

Cyanide poisoning, Cyanide toxicity, Cyanide toxicosis and Formic anamminide or Formonitrile and Prussic acid poisoning (WHO, 2004; Ballantyne and Salem, 2008).

**Physio-chemical properties of Cyanide**

Cyanide exists in various forms including gaseous HCN, water soluble potassium cyanide and sodium cyanide, poorly water soluble mercury, copper, gold and silver cyanide salts. Hydrogen cyanide (HCN) is a colorless or pale blue liquid or gas with a faint bitter almond-like odour. HCN is having liquid state at NTP (normal temperature and pressure), poor ionization, low molecular weight, low boiling point, high vapour pressure, low vapour density, and hence ready diffusibility. HCN is a weak acid with a pKa of 9.22 at 25°C; therefore, HCN and CN– can interconvert based on pH and temperature. Sodium cyanide (NaCN) is a white hygroscopic crystalline powder, whereas potassium cyanide (KCN) is a white deliquescent solid. Calcium cyanide (Ca(CN)2), or calsyan, is a white crystalline solid and Cyanogen chloride is a colourless gas, heavier irritating and pulmonary acting (WHO, 2004; ATSDR, 2006; EPA, 2010; Ballantyne and Salem, 2008). Cyanide has relatively more affinity for metal (Fe3+, ferric). It is salts like sodium cyanide will liberate highly toxic gas upon contact with water including moist air and acidic media.

**Source of poisoning**

Animals are more frequently exposed to cyanide through ingestion of plants containing cyanogenic glycosides (Nobrega et al., 2006). Cyanide occurs naturally as cyanogenic glycosides in about 2000 plant species (JECFA, 1993). At least 55 cyanogenic glycosides are known to occur in plants, many being synthesized from amino acids as part of normal plant metabolism (Knight and Walter, 2002). Commonly important cyanogenic glycosides found in plants, are dhurrin (Sorghum spp.), linamarin (cassava, linseed meal), taxiphyllin (Bamboo shoots) and amygdalin (almonds) (JECFA, 1993). Most common source of cyanogenic plant poisoning in India, is feeding of immature sorghum i.e. young shoots of Sorghum vulgare and Sorghum sudanense to livestock or accidental ingestion of pods of Acacia leucocephalaby to sheep and goats (Vadlamudi, 2000). Free HCN is liberated from glycosides by the action of mastication, chewing or enzymatic action of certain enzymes like beta-glucosidase and hydroxynitrile lyases. These enzymes are widely distributed in the same plant or in bacteria of animal digestive system (Clarke et al., 1981). In most cases, hydrolysis is accomplished by the beta-glucosidase, producing sugars and a cyanohydrin that spontaneously decomposes to HCN and a ketone or aldehyde. This step can also be catalyzed by the enzyme hydroxynitrile lyase, which is widespread in cyanogenic plants (Harborne, 1993; Gruhnert et al., 1994). Selective breeding of certain varieties of plant species with naturally low glycoside content has resulted in varieties that are low in cyanogenic glycoside; and has increased their food value for humans and animals. Sorghum varieties low in cyanide has been developed that have greatly increased the safety of feeding sorghum, such as Sudangrass, to livestock (Knight and Walter, 2002). Cassava has increasingly been used to replace corn in feeding livestock to lower the cost. Cassava tuber contains cyanogenic glycosides, known as
linamarin and lotaustralin that could cause toxicity. As a consequence, the animals are exposed to low but constant amounts of cyanide for prolonged periods (Tewe, 1992). Cyanide can also cause poisoning by inhalation of cyanide-containing gas (such as hydrogen cyanide or cyanogen chloride) or dust containing solid or liquid cyanide. Typical sources are industrial (e.g. in gold and silver mining, x-ray film development, fumigation of ship acrylic manufacturing, electroplating, jewellery manufacturing, steel fabrication and warehouses vermin eradication), or combustion of plastics, acrylics, synthetic rubber, carpeting or upholstery in enclosed spaces. Iatrogenic exposure can occur through overdose of sodium nitroprusside (Meredith et al., 1994; Nicholson, 2007; Barillo, 2009; Leybell et al., 2011). Cyanides due to their rapid lethal toxicity, they have been used for suicide, homicide, judicial execution, and chemical warfare operations. Also, there is risk of cyanide salts being used as an agent for terrorist attack (Ballantyne and Salem, 2008).

**Lethal dose**

Acute oral LD$_{50}$ values for HCN in starved and un-starved female rats is reported 3.08 mg/kg and 4.21 mg/kg, respectively (Ballantyne and Salem, 2008). The lethal dosage of HCN in most animal species is in range of 2 mg/kg to 2.5 mg/kg (Clarke et al., 1981; Knight and Walter, 2002; Schneider, 2012). Minimum lethal dose of HCN for sheep and cattle is about 2 mg/kg body weight, when taken in the form of glycoside (Radostits et al., 2007). LD50 value for cyanide is reported 5.3 and 6 mg/kg body weight in dog and cat, respectively (Shlosberg and Booth, 2006). Cyanide poisoning is related to the amount of forage consumed and the animal’s physiological condition, but HCN levels exceeding 220 ppm on a wet weight (as is) basis are dangerous. Forage containing <100 ppm HCN, wet weight, is usually safe to pasture (Schneider, 2012). On a dry weight basis analyses, forages with more than 500 ppm HCN should be considered potentially toxic (Fjell et al., 1991).

**Species Affected**

Ruminants are more susceptible to cyanogenic plant toxicity as compare to monogastric animals (horses and swine) and cattle slightly more so than sheep. Hereford cattle have been reported to be less susceptible than other breeds (Schneider, 2012). Ruminants are more susceptible because of the normally mildly acidic to alkaline rumen contents (pH 6.5 – 7.0), high water content, and microfloral enzymes in the rumen hydrolyze the cyanogenic glycosides to HCN (Knight and Walter, 2002). Dogs have a relatively low amount of the detoxifying enzyme rhodanese and are more susceptible to acute effects of cyanide toxicity as compared to other mammals (ATSDR, 2006).

**Other Factors influencing cyanide poisoning in animals**

Grain sorghums are potentially more toxic than forage sorghums or sudangrass, whereas hybrid pearl millet and foxtail millet generally have very low cyanide levels (Fjell et al., 1991). Stage of growth of plant also affects its cyanide concentration. Young or immature plant or rapidly growing plants after draught has highest cyanide toxic concentration. Drying or silage preparation decreases the cyanide contents. Any physical damage to plant tissue such as freezing (frost), crushing, macerating (rumination), cutting and drying, allows plant enzymes to come in close
contact with and resulting in more hydrolysis to release more free HCN (Nicholson, 2007). During draught period, the concentration of cyanogenic glycoside increases. Wilted forage or forage with high free cyanide content is more toxic than forage with intact seeds and leaves (Osweiler, 1996 and Fitzgerald, 2006). Excessive use of nitrogen fertilizers and weedicides like 2-4 D may increase HCN concentration in plants. High soil content of nitrogen and low phosphorus is favorable for high cyanide content in plant grown there (Vadlamudi, 2000). Ruminal microorganisms have the capacity to degrade cyanogenic glycosides and an intra-ruminal release of HCN does not require the presence or action of plant enzymes. This non-enzymatic pathway is pH-dependent. Rate of dissociation of cyanohydrins in ruminal fluids was found to be high at pH more than 6 (Majak et al., 1990). Higher pH increases the rate of conversion of cyanogenic glycoside to HCN and thereby greaten the risk. Water drunk after animals have eaten cyanogenic plants enhances the hydrolysis of the glycosides. Conversely, ruminants that are on high energy grain rations where the rumen is more acidic (pH 4 - 6) have a slower release of HCN than if they were fed a grass, hay, or alfalfa diet (Majak et al., 1990; Knight and Walter, 2002).

**Toxicokinetics**

Cyanide is rapidly absorbed from the gastrointestinal tract once released from cyanogenic glycoside. It is also rapidly absorbed from lungs after inhalation but relatively slow absorbed from skin after dermal exposures. Following oral absorption, cyanide is quickly and widely distributed to all organs and tissues of the body with more concentrations in liver, blood, lungs, brain and kidney. Cyanide has not been shown to accumulate in the blood and tissues following chronic oral exposure to inorganic cyanides (ATSDR, 2006; Sandhu and Brar, 2009). Hydrogen cyanide, with a pKa value of 9.22, is distributed in the body as hydrogen cyanide and is not present as the free cyanide ion at physiological pH. So, form of cyanide exposure or its salt type does not influence distribution, metabolism, or excretion from the body (ECETOC, 2007). The bio-detoxification of cyanides occurs through several pathways, of which the main is metabolism of cyanide to the less toxic thiocyanate (SCN), and is responsible for conversion of up to 80% of a cyanide dose. Cyanide is transformed to thiocyanate in the body, with a plasma half-life of 20 minutes to 1 hour. Two enzymes responsible for this transulfuration process are thiosulfate–cyanide transulfurase (also known as rhodanese) and beta-mercaptopyruvate–cyanide transulfurase. Mitochondrial enzyme rhodanese is responsible for primary metabolism of small quantity of cyanide (ATSDR, 2006; Ballantyne and Salem, 2008). For most species, rhodenese activity is high in liver, kidney, brain, muscle, but also reported to be found in respiratory and gastrointestinal systems (Aminlari and Gilanpour, 1991; Aminlari et al., 1994). This enzyme, at the approximate rate of 17µg/kg/min catalyzes the irreversible reaction of cyanide and a sulfane to produce thiocyanate, a relatively nontoxic compound excreted in the urine (HSDB, 2013). Rhodanese or Thiosulfate sulfurtransferase (TST) is a mitochondrial enzyme encoded by the TST gene that converts cyanide to the far less toxic metabolite, thiocyanate (Parkinson and Ogilvie, 2008). The reaction involves transfer of sulfur from endogenous thiosulfate, or any
other sulfur donor which must have sulfane sulfur i.e. one sulfur bonded to another sulfur. The sulfite produced by this reaction can be converted to sulfate by the molybdozyme, sulfite oxidase. During conversion by rhodanese, a sulfur atom is transferred from the donor to the enzyme, forming a persulfide intermediate. The persulfide sulfur is then transferred from the enzyme to cyanide, yielding thiocyanate. Thiocyanate is then readily excreted in the urine as the major metabolite. Other minor metabolic pathways proposed for cyanide are: (1) conversion to 2-aminothiazoline-4-carboxylic acid, (2) incorporation into a 1-carbon metabolic pool or (3) combining with hydroxocobalamin to form cyanocobalamin (vitamin B₁₂). Once thiocyanate is formed, it is not converted back to cyanide. Cyanide is eliminated unchanged from the body in breath, sweat, and urine as sodium thiocyanate in the urine and as iminothiocarboxyllic acid (ITCA) from reaction with sulfhydryl groups (Krenzlok, 2003; ATSDR, 2006). Sousa et al. (2003) determined the effect of the species like rats, pigs and goats on the toxicokinetics of cyanide and its main metabolite, thiocyanate. The elimination half-life and volume of distribution of both cyanide and thiocyanate were higher in goats (1.28 and 13.9 h, and 0.41 and 1.76 l/kg, respectively). They hypothesized that metabolism of cyanide and its main metabolite, thiocyanate, is species-linked, with the goat being more sensitive to the toxic effects of cyanide/thiocyanate. Offsprings that suckle from dams exposed to cyanogenic plants can be affected, as thiocyanate and possibly cyanide can be transferred from the maternal bloodstream to the kids via the milk, thus, indirectly intoxicating the offspring (Soto-Blanco and Gorniak, 2003).

Toxicodynamics

Cyanide ion has a high affinity for ferric (trivalent) iron in the cytochrome oxidase system and combines with it. This causes blocking of electron transport and molecular oxygen transfer from oxyhemoglobin to tissues, resulting into reversible cellular hypoxia or histotoxic anoxia (Nicholson, 2007) thus, tissues with higher oxygen demands suffer greatly in cyanide poisoning. Cytochrome c oxidase, a metalloenzyme is inhibited by cyanide ion to produce its acute toxic effects (Way, 1984). Cytochrome c oxidase (CcO or complex IV) is the last enzyme (terminal oxidase) in the respiratory electron transport chain located in the bacterial mitochondrial membrane. In bovines, this large transmembrane protein complex contains two hemes (iron sites) i.e. cytochrome a (haeme a) and cytochrome a₃ (haeme a₃), and two copper centers, the Cuₐ and CuₐB centers (Tsukihara et al., 1995). Cytochrome a₃ is the site for oxygen (O₂) binding when it is in the reduced state and acts as the O₂ reduction site in conjunction with CuB which is located nearby. Fully reduced CcO has unusually high affinity to CN⁻ and not HCN. Cyanide (CN⁻) bound form undergoes a fairly large conformational change in the O₂ reduction site (Yoshikawa et al., 2012), hence, blocks electron transport resulting in decreased oxidative metabolism and oxygen utilization even in the presence of adequate oxygen stores. The decreased O₂ causes oxygen tensions to rise in peripheral tissues resulting in decreased unloading gradient for oxyhemoglobin and thus, oxyhemoglobin is carried in the venous blood (ATSDR, 2006). Death occurs
due to depression of central nervous system (CNS), subsequent to inhibition of brain cytochrome oxidase activity (Way, 1984). Linamerine is cyanogenic glycoside which is metabolized to cyanide and cyanate in body. These are responsible for causing memory loss and cognition deficit in rodents (Kimani et al., 2014).

**Target organ toxicity in animals**

Nervous system is primary target of cyanide toxicity due to anaerobic metabolism, low energy reserve and high energy demand (Hariharar Krishnan et al., 2010). Respiratory and cardiovascular systems are other target. Gastro-intestinal, hepatic, renal, endocrine, hematological, musculoskeletal and teratogenic effects are also observed (ATSDR, 2006). Cyanide induced histotoxic hypoxia is characterized by depletion of cellular ATP and concurrent destabilization of ionic homeostasis. Rapid rise in calcium ion (Ca$^{++}$) concentration plays important role in cyanide toxicity. Increased calcium concentration activates calcium sensitive enzymes like protein kinase C (PK-C), phospholipase A$_2$ (PLA$_2$) and neurotransmitter secretion. Acute cyanide toxicity depletes gamma butyric acid (GABA) and dopamine, and elevates glutamate level in different brain regions (Persson et al., 1985), followed by Ca$^{++}$ influx through voltage-gated as well as glutamate-gated channels. As they express Ca$^{++}$-activated NOS (calcium-dependent nitric oxide synthases), neurons are also prone to generate “nitrosative stress”, which affects not only themselves but perhaps more significantly the neighboring astrocytes (Szab’o, 1996). Soto-Blanco et al. (2002) reported that chronic cyanide exposure can promote neurophathological lesions like gliosis in goats. In addition, cyanide seems to have a prominent vasoconstrictor effects (Brierley et al., 1976). This increases its toxic effects in brain and cardiovascular system. Cyanide can also produce multiple endocrine effects including epinephrine and histamine release (Baskin, 1997). Necrosis is the most prevalent central nervous system effect following acute duration exposure to high concentrations of cyanide, whereas demyelination is observed in animals at repeated exposures of sub-lethal concentration (ATSDR, 2006). Prolonged cyanide exposure has been associated with disturbances of thyroid metabolism in pigs (Tewe et al., 1984) and goats (Soto-Blanco et al., 2001). Goats receiving high dose of cyanide showed lower body weight gains and a decrease in plasma T$_3$ concentrations. Behavioral changes have also been reported in goats following sub-lethal cyanide intoxication with delayed signs of toxicity (Soto-Blanco et al., 2005). Developmental defects were observed in cows (Seaman et al., 1981) associated with cyanide, whereas Selby et al. (1971) reported fetal malformations in swine. Pregnant sows having access to the cyanogenic wild black cherries (Prunus serotina) farrowed piglets with atresia ani, rudimentary external genitalia and skeletal defects. Manzano et al. (2007) in a study revealed that long-term administration of cyanide to pigs promotes neurotoxic, hepatotoxic and nephrotoxic effects, while the thyroid gland and pancreas remained unaffected. Kamalu (1993) also reported hepatotoxicity and nephrotoxicity in growing dogs fed on cassava (cyanide rich plant).

**Clinical findings**

Generally, signs quickly develop within 10 minutes to one hour in acute cyanide intoxication including hyperventilation, decreased blood
pressure, hypoxemia-induced convulsions, coma, shock, respiratory failure and death. The progression after the onset of convulsion is rapid and animal has characteristic bright cheery red colored mucous membrane (Plumlee, 2004). In small animals, acute cyanide intoxication is much more common than chronic poisoning. Early signs include tachycardia, hyperpnea, and dyspnoea whereas later signs include nausea and vomiting, hypotension, generalized seizures, coma. Dilated pupils (either sluggish or totally non-reactive) and cardiac effects like tachycardia, bradycardia, ventricular arrhythmia, erratic supraventricular arrhythmia, ischemic changes on ECG, atrioventricular blocks and eventual asystole are observed in small animals (Fitzgerald, 2006). Ruminants may exhibit signs within minutes to less than an hour after commencing ingestion of toxic plant material which includes apprehension, pronounced polynepa then dyspnea, because initially there is stimulation of chemoreceptors in the carotid body and respiratory centers (Nicholson, 2007). Ingestion of moderate quantity of cyanogenic plants in cattle results in tympanism (bloat), ataxia, dyspnea, paddling movements and convulsions, collapse and falling to ground (Lorgue et al., 1996). The earliest signs after cyanide exposure are due to dysfunction in neurons and in the myocardium which may commonly manifested as collapse with hypotension or tachycardia. The goats suffered with acute cyanide toxicosis were found depressed, tachycardic, and had marked jugular pulses. The goats that died collapsed shortly before death (Tegzes et al., 2003). Sub-lethal cyanide intoxication in goats resulted in transient clinical signs which included depression and lethargy, mild hyperpnoea and hyperthermia, arrhythmias, abundant salivation, vocalizations, expiratory dyspnoea, jerky movements and head pressing; and convulsion later on in some animals (Soto-Blanco et al., 2005). After grazing forage sorghum and grain sorghum re-growth, breeding cows became ataxic and developed urinary incontinence (McKenzie and McMicking, 1977). Typical clinical signs of cyanide poisoning like dyspnoea, anxiety, restlessness, tympany, signs of colic, excitement, hypersalivaton, bright red coloured mucuos membranes, dilated pupils, staggering gait as well as tremors were reported in crossbred cows fed with immaturely cut sorghum grass in pre-monsoon season (Patel et al., 2012). Three aged cows showed signs of anorexia, weakness, depression, stupor, circling, bruxism, excessive salivation and tenesmus; when approached they were aggressive. They showed ruminal stasis, bright red mucous membranes, tachycardia with cardiac dysrhythmia, tachypnoea and scant tarry faeces (Sargison et al., 1996). Horses (three out of 11) after being fed on Sorghum vulgare for over 2 months showed incoordination of the hind legs, developed frequent urination, urinary incontinence and haematuria, followed by a serious nasal discharge, increased body temperature, depression and reduced appetite (Varshney et al., 1996). Leucomyelomalacia (cystitis-ataxia syndrome) in ruminants and horses is attributed to chronic cyanide intake (Radostits et al., 2007). An outbreak of poisoning by Sorghum halepense in cattle in the Brazilian semi-arid was reported. Clinical signs of dyspnoea, anxiety, muscle tremors and incoordination appeared 15 minutes after the animals began to graze (Nobrega et al., 2006).
Postmortem Findings

Mucous membranes colour is pink in cyanide toxicity whereas venous blood is bright red which may clot slowly. Subendocardial and subepicardial petechial and ecchymotic hemorrhages typical of an agonal death may be present. A “bitter almond” or “cherry coke” odor from stomach contents may be detectable. Venous blood may not be bright red in animals dead several hours (Nicholson, 2007). The ability to detect odour of bitter almonds is genetically determined, and many people cannot do so (Fitzgerald, 2006). Cyanotic mucosa, dark muscles, lung edema and hemorrhages were observed at postmortem of died cattle (Nobrega et al., 2006). In cattle, wallerian degeneration of the white matter of the spinal cord, cerebellar peduncles and cerebellum was reported (McKenzie and McMicking, 1977).

Differential diagnosis

Differential diagnosis of cyanide poisoning in ruminants may include acute toxicoses caused by nitrate–nitrites, urea–ammonia, ipomeanol, bluegreen algae, electrical shock or lightning strike, acute pulmonary oedema, anaphylaxis and goiter (Nicholson, 2007; Radostits et al., 2007).

Laboratory findings

For confirmation of diagnosis, samples of stomach contents, or skeletal muscle, should be immediately frozen in airtight containers (as HCN is volatile in nature), and shipped frozen to an appropriate laboratory. Specimens can be immersed in mercuric chloride to prevent hydrolysis of glycosides and loss of HCN (Nicholson, 2007). Low concentrations of cyanide in tissues are indicative of intoxication. Severe metabolic acidosis (elevated blood lactate or reduced blood pH) together with an increased anionic gap are indicative. Whole, heparinized blood samples collected in airtight containers with no air space (submitted immediately or frozen) can also be analyzed for cyano-haemoglobin or cyanide. As there is an affinity of cyanide to bind to erythrocytes, the spleen may contain elevated cyanide concentrations (Shlosberg and Booth, 2006). HCN concentrations more than 1, 1.4 and 10 ppm in blood, liver and ruminal content respectively, are suggestive of cyanide poisoning (Clarke et al., 1981, Burrows and Tyrl, 2013). Alkaline picrate treated filter paper strips can be used for testing plant materials and fresh rumen contents by modified Guignard test (Burrows and Tyrl, 2013). This is a sensitive and qualitative test popularly known as Picrate Paper test. Commercial field kits are also available.

Treatment

Treatment must be initiated on emergency basis. After decontamination and life support measures is started, the key to treatment of cyanide poisoning is early administration of an antidote. The decision to administer the antidote often is made empirically. The antidote of choice in most of animals is combination of sodium nitrite and sodium thiosulfate (also known as sodium hyposulfite or ‘hypo’). The sodium nitrite act as methemoglobin forming agent and is administered to form methemoglobin and bind cyanide. Amyl nitrite is another methemoglobin forming agent used alone or with sodium nitrite. Sodium thiosulfate is administered in combination with the nitrates to clear cyanide by acting as a sulfhydryl donor. The unbound, extracellular cyanide binds with sulfur of thiosulfate to form the renally excreted thiocyanate. Successful dose regimen includes rapid IV
infusion of 5 g sodium nitrite and 15 g sodium thiosulfate in 200 ml water for cattle, and 1 g sodium nitrite and 3 g sodium thiosulfate in 50 ml water for sheep (Radostits et al., 2007). Ruminants can be treated with thiosulfate alone using a 30–40% solution intravenously at a dose of 25–50 g/100 kg body weight (Nicholson, 2007). However, the improved results in ruminants were observed by using heavier doses of Sodium thiosulfate (660 mg/kg b.wt.) alone or combined with high dose of sodium nitrite (22 mg/kg BW) (Burrows and Way, 1979). However, for treatment of cyanide intoxication of ruminants, doses of sodium nitrite should be smaller than those recommended for other animals because ruminants are more susceptible to the toxic effects of sodium nitrite. Treatment with any choice of regimen should be repeated because of further liberation of HCN. Non-specific supportive treatment, including respiratory stimulants and artificial respiration are unlikely to have any effect on the course of the disease. Total 150-200 g sodium thiosulfate is also advocated orally in cattle. Oral doses of 30 g of sodium thiosulfate repeated at hourly intervals are also given orally to cattle (Radostits et al., 2007). Another treatment protocol advisable for cattle (Lorgue et al., 1996) includes sodium hyposulphite (3g/100 kg i.v.), 10 % sodium nitrite solution (15 ml/ 100 kg i.v.) and dicobalt edentate (20-25 mg/kg i.v.). The combination of cobalt salts (Cobaltous chloride) and oxygen with the traditional sodium nitrite-sodium thiosulfate antidote may have some protection value against cyanide poisoning (Burrows and Way, 1977). A new antidote, sulfanegen sodium, a prodrug of 3-mercaptopyruvate, resulted in progressive significant reduction in blood lactate and CN levels with 100% survival in a juvenile pig model. Severe CN toxicity was induced by sodium nitroprusside and sodium cyanide administration, and at peak toxicity, the animals were given sulfanegen sodium (2.5 g IV, repeated every hour) (Belani et al., 2012). It is also important to administer the antidotes slowly and take utmost care to prevent their overdosing because they are associated with morbidity and even mortality. Hydroxocobalamin is also another promising antidote which is approved by the Food and Drug Administration for human use in December, 2006. Hydroxocobalamin (vitamin B_{12a}), the natural form of vitamin B_{12}, is a hemelike molecule with a complexed cobalt (Co) atom. It combines with cyanide to form nontoxic cyanocobalamin (vitamin B_{12}) which is excreted in the urine. Hydroxocobalamin reversed cyanide toxicity and reduced mortality in a canine model (Borron et al., 2006). Vikhyat et al. (2013) compared the therapeutic efficacy of hydroxocobalamin (65 mg/kg) and cobinamide (12.5 mg/kg) in pigs with induced cyanide toxicity. Both the anti-dotes lowered blood cyanide to undetectable level immediately after treatment and respiratory distress disappeared soon.

**Supportive therapy**

Oral therapy with glucose, molasses, or glyceraldehyde may provide a benefit. These products act as slow antagonists by tying up free HCN into cyanhydrin. However, due to the slow nature of this detoxification, they should not be used as a primary treatment (Burrows and Tyrl, 2013). Saturated jaggery solution along with standard antidotal treatment was found to be synergistic for early recovery of animals (Patel et al., 2012).
Control and prevention

Various preventive measures are suggested for livestock owners to reduce the incidences of cyanide poisoning in animals: (i) Ensure animal graze only old sorghum and avoid new growth, (ii) Medium strength nitrate fertilizers should be used with manure which has high phosphate level (Lorge et al., 1996), (iii) Animals should be restricted from grazing sorghums during early re-growth after the plants have been cut, droughted, or frosted, (iv) Allowing sorghum forages to grow at least 2 feet high before allowing animals to graze them, (v) Hay making and ensilaging reduces the cyanide content, (vi) Hybrid varieties (sudan-grass x sorghum) and selected forage sorghums that have been specifically developed for low cyanogenic glycoside content should be used as forage crops (Knight and Walter, 2002), (vii) The pH in the stomach plays a major role in the hydrolysis of the cyanogenic glycoside. Lowering the stomach pH by feed management and supplements reduces the risks from cyanogenic forage, and (viii) Sulphur supplements in salt can also be used to increase the rate of natural detoxification and resistance (Burrows and Tyrl, 2013).

CONCLUSION

Cyanide being a potent inorganic poison and having wide distribution in environment causes incidences of toxicity in domestic animals. The early diagnosis and treatment with sodium thiosulphate and sodium nitrite is being used widely along with supportive therapy like oxygen therapy, cobalt salts, hydroxyl cobalamin etc. A newly developed antidote ‘Sulfenegen’ has been proved 100 per cent effective in reducing blood cyanide level and protecting all the pig exposed to cyanide. The clinical implementation of this newly developed antidote would pave the new avenue for the treatment of cyanide toxicity. The Scientific feeding and grazing management prevents occurrence of cyanide toxicity.

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