LONG TERM EXPOSURE TO CHEMICALS, INSECTICIDES AND HEAVY METALS
CAUSING TOXICITY: A REVIEW

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Abstract

Insecticides are used worldwide for crop protection especially in the developing nations. Neonicotinoid insecticides, which are one of the most important classes of commercial insecticides worldwide are systemic in plants and animals and are used to manage crop pests and control fleas on cats and dogs. Acetamiprid belongs to the class of chloronicotinyl neonicotinoid insecticides used to control insects and ectoparasites viz., Hemiptera, particularly aphids, thysanoptera and lepidoptera on a wide range of crop species. The indiscriminate and injudicious use of second generation fluoroquinolones viz., enrofloxacin produced anemia, leucopenia, hypoglycaemia, hypoproteinemia, increased enzymatic activity and hepatotoxic and nephrotoxic effects in broiler chickens. Exposure to heavy metals results in congestion and hemorrhages in the lungs, tubular degeneration in kidneys and occasional hemorrhages in the brain. The present article was conducted to review the various pharmaceutical, physiological and toxicopathological effects of different chemical agents and heavy metals due to environmental exposure and through feed on poultry birds. Heavy metals possess high density and toxicity towards living beings. Heavy metals like arsenic, chromium, lead and mercury are point popular and relevant. Heavy metals constitute the crust of the earth which resists degradation. Human get inflicted with heavy metals through the agency of food, water and atmosphere. Mercury poisoning by eating fishes is a prominent cause for public health hazard.

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Introduction

Neonicotinoid insecticides, which are one of the most important class of commercial insecticides worldwide, are systemic in plants and animals are used to manage crop pests and control fleas on cats and dogs. The selective toxicity of neonicotinoids is attributed for nicotinic acetylcholine receptors of insects to that the mammals to the fundamental differences between the receptors. Whereas nicotine binds at an anionic subside in the mammalian nicotinic Ach receptors, the negatively tipped (Magic nitro or Ciano) neonicotinoid interact with a proposed unique subside consisting of cationic amino acid residues in the insect nicotinic Ach R. Nicotine and imidacloprid share the same structural moiety, the same mode of action, and essentially the same structural activity relationships. Several analogs including acetamiprid, thiamethoxam and thiacloprid, have since been discovered and have been shown to have the same mode of action as imidacloprid. Neonicotinoid are those compounds which have an essential moiety like nitroimine, cyanoimine or nitromethylene.¹

Enrofloxacin is a second generation quinolone derivative which belongs to the group fluoroquinolone. The fluoroquinolones are metabolized in the liver and excreted in urine through the kidney. The liver and kidney develop the highest drug concentration though concentrations in essentially all tissues, including the skeletal and central nervous system reach therapeutic levels. That is why it is relevant to detect the pathological alteration in the visceral tissues and organs.

Selenium function is closely associated with Vitamin E. Both have antioxidant property and protect the biological membranes from oxidative degeneration. Glutathione peroxidase is the enzyme which has selenium as its constituent with 4 gm Se atoms per mole. Out of the total body selenium, 40 per cent is in the enzyme glutathione peroxidase as observed in rats. Both glutathione peroxidase and vitamin E prevent the formation of lipid hydroperoxides which damage the
cellular membrane and disturbed the structural integrity of the cells. Selenium and vitamin E are mutually replaceable to some extent but up to a particular limit.\textsuperscript{2,3,4}

Fish serves as an important and rich source of easily digestible protein supplement to our body. Also fish oil serves as an important source of omega-3 fatty acids also contains traces of mercury, as reported by the Environmental Protection Agency. Mercury generally does not pose its deleterious effect alone. It combines with carbon to form organic compounds, like methylmercury. It is formed in water and soil as per reports of while diets should include fish as part of a nutritional regimen, this protein source rich in omega-3 fatty acids also contains traces of mercury, as put forth by the Environmental Protection Agency. Mercury, a metal that exhibits several forms, combines with carbon to form organic compounds. The most familiar one is methylmercury, which is created by microorganisms found in soil and water as per reports of the \textit{Agency for Toxic Substances and Disease Registry}. Methylmercury generally accumulates in the fish muscles on over exposure.\textsuperscript{5}

\textbf{Research reports and findings}

Cases of acute ciprofloxacin toxicity of birds have been reported earlier by many investigators\textsuperscript{6,7}, in human\textsuperscript{8} and in broiler birds\textsuperscript{9}. Birds treated with therapeutic dose develop mild diarrhea and depression which simulated the reports\textsuperscript{6,7}. Broiler birds of control group had no clinical manifestation at any stage during the experimental period.

Anemia in human treated with ciprofloxacin has been reported\textsuperscript{6,8}. Broiler birds treated with ciprofloxacin develop leucopenia\textsuperscript{9}. Hypoproteinemia in broiler birds treated with overdoses of ciprofloxacin was reported\textsuperscript{4}.

Niyogi\textsuperscript{9} and Sugawara et al.\textsuperscript{10} also reported an elevated serum enzymatic activity in broiler birds and monkey respectively after therapy with ciprofloxacin both in therapeutic dose and higher doses of the drug. An increased level of serum enzymatic activity is known to occur in a wide range of inflammatory/degenerative
disease conditions particularly in hepatic and nephrotic diseases. An experimental study was conducted by Niyogi et al. to estimate the residual concentration of arsenic in different tissues/organisms of broiler birds induced with arsenic trioxide @ 1/10th of acute LD$_{50}$ i.e. 16.25 mg/kg bw 6 weeks. All the induced birds had widespread distribution of arsenic in the organs/tissues. However, the residual concentrations were not uniform in various tissues, possibly due to variation in the rate of accumulation and/or clearance of residues from the individual tissues/organs. The largest residual concentration of arsenic was found in liver, next largest in proventriculus, followed by intestine, kidneys, feather, skin, spleen, bursa of Fabricius, skeletal muscles, heart, lungs, brain and lowest in the blood. In this study, control birds had least amount (0.02-0.39 μg/g) of arsenic in various organs or tissues, possibly due to environmental contamination. The accumulation of arsenic in organs/tissues of treated birds varied from 0.124-36.89 μg/g of wet tissue which was abnormally higher than the values in the tissues of normal birds.$^{11}$

Salyi et al.$^{12}$ induced acute experimental selenium poisoning in broiler chicks and concluded that oral LD$_{50}$ of selenium in the form of sodium selenite was 9.7 mg/kg body weight. Earlier workers have reported significant decline in body weight of selenium fed chickens. The organic form of selenium is known to be accumulated in higher quantities and persist for longer periods in tissues as compared to inorganic toxicity$^{13-15}$. Increasing trends in the liver concentration of selenium in chicks, hens, cockerels and sheep have been reported by other workers.$^{12-14}$

According to Cousins and Cairney, the increased intake of selenium resulted in steady rise in tissue selenium concentrations until levels as high as 5-7 ppm in liver and kidneys.$^{16}$

Paul et al. conducted with sixty healthy day old broiler chicks to determine the effect of induced enrofloxacin toxicity. The birds were divided into four groups keeping the first group as control. Clinically, the broiler birds in all the
treatment groups administered with therapeutic dose of enrofloxacin expressed the clinical symptoms of systemic toxicity. Hematological studies indicated that the hemoglobin concentration, packed cell volume, total erythrocytic count and total leucocytic count showed significant variation (P<0.01) between the treatment groups. Biochemically, all treated groups of birds induced with graded dose level of enrofloxacin, had significantly (P<0.01) decreased levels of total plasma protein with simultaneous reduction in albumen-globulin (A:G) ratio than in controls. Acetamiprid is a broad spectrum, high effective, safety, insecticide with good contact and stomach poisoning to pests, activity. As neonicotinoids insecticides persist in crops, biotransformation of these insecticides represents a promising approach for improving the safety of food. The neonicotinoids possess common characteristics that distinguish them from conventional insecticides suggested that after uptake of imidacloprid by sucking pests, feeding ceases and an avoidance behavior results.

Clinical signs

Acetamiprid having low hazards for mammals and high potency to pests, are essential requirements for safe and effective pesticides though few studies has done at different dose levels in rats, goat, bees, mice etc. However in mammals poisoning of neonicotinoid insecticides may cause trembling, emaciation, staggering, labored breathing, apathy, convulsion etc.
Dilation of pupils, weakness, paralysis of hind legs, gasping and tonic clonic convulsions were also observed.¹

**Hematological reports**

There are reports of reduction in RBC count and PCV in rat’s when cypermethrin and permethrin were administered at a single dose of 10mg/kg b.wt of each pyrethroid. A significant increase counts in white blood cells (WBCs) is noticed in male mice treated with these insecticides, while RBCs decreased when the animals were treated with formulated insecticides. Reduction in hemoglobin concentration and the hematocrit values in general takes place. All three insecticides caused a significant increase in the mean cell volume.¹

**Pathomorphological studies**

Gross changes in liver of insecticide treated birds show enlarged, pallor or yellowish discoloration. Marked areas of hemorrhages necrosis, congestion, and fatty changes were also observed, congestion of upper respiratory tract and myocardium, mild enteritis in small and large intestines in all treated birds. Histopathologically, significant alterations in the liver is observed, such as mild fatty changes, congestion and degeneration of hepatocytes, in kidneys including marked congestion, tubular cell degeneration and sloughing of epithelial cells. The cerebral hemisphere revealed changes comprising of mild neuronal degeneration with surrounding glial cells, satellitosis and vacuolation. Mild congestion and hemorrhages is also observed in lungs and myocardial tissues following oral administration.

Mondal studied the pathology of induced acetamiprid daily orally for a period of 28 days at the dose rate of 25, 100, and 200mg/kg b.wt respectively and observed liver is the most affected organ followed by lungs, heart, spleen, brain, kidney and ovary. In heart there was hemorrhage, degenerative and necrotic changes in cardiac muscles cells, heart showed edema, mild hemorrhages in epicedium and edema at higher dose i.e. 200mg/kg wb/wt/day.¹⁷ Bhardwaj et al. administered imidacloprid orally daily to female rats for a period of 90 days with doses of 0,
5, 10, 20mg/kg/day. And observed hepatocellular damage in the higher dose treated animals. Repeated exposure of high dose of imidacloprid (20mg/kg/day) for 90 days produced mild focal necrosis with swollen cellular nuclei and cytoplasmic lesions in the hepatocytes of liver. There were slight degeneration of tubules and glomeruli of the kidney of female rats compared with control and also resulted to necrosed Purkinje cells with loss of dendrites and granules in granular layer of cerebellum. However, no pathological changes were observed in brain, liver and kidney of rats exposed to imidacloprid at 5 and 10mg/kg/day.18

Goyal et al. studied the histopathological alterations induced after oral sub acute thiacloprid toxicity in Gallus domesticus on repeated oral administration of 10mg/kg/day thiacloprid for 28 days. Results showed that gross changes in liver of treated birds with enlarged, pallor or yellowish discoloration. Marked areas of hemorrhages necrosis, congestion, and fatty changes were also observed, congestion of upper respiratory tract and myocardium, mild enteritis in small and large intestines in all treated birds. Histopathologically, significant alterations in the liver were observed, such as mild fatty changes, congestion and degeneration of hepatocytes, in kidneys included marked congestion, tubular cell degeneration and sloughing of epithelial cells. The cerebral hemisphere revealed changes comprising of mild neuronal degeneration with surrounding glial cells, satellitosis and vacuolation. Mild congestion and hemorrhages was observed in lungs and myocardial tissues following oral administration of thiacloprid. Zhang et al20 investigated the short term toxicity of acetamiprid in male mice which showed vacuolation of the seminiferous tubules, number of spermatids, and interstitial Leydig cells were obviously decreased. Moreover some cells sloughed from the lumen of the seminiferous tubules, some primary spermatocytes vacuolated with widened interstitium.

The effect of consumption of mercury toxicity is immense on human health. It primarily affects the kidneys and brain...
of growing fetus. Poisoning due to mercury can cause injury not only to the brain and kidneys but also to a growing fetus. The Agency for Toxic Substances and Disease Registry has reported the toxic effect of mercury on primarily the human nervous system and that of growing fetus in particular. Contact with the metal causes difficulties with memory and distortions in hearing and vision including tremors and irritability. As per reports of EPA and FDA, the toxicity from heavy metals due to fish consumption According to the EPA, the dangers of mercury poisoning from eating fish are not a major concern. The risk depends on the amount of fish intake coupled with levels of mercury in the fish. EPA and FDA recommends pregnant and nursing mothers to avoid the consumption of such type of infected fishes and are recommended for intake of fish low in mercury content.⁵,²¹

Conclusion

Insecticide chemicals and heavy metals possess basic and clinical toxicity towards living beings. Heavy metals constitute the crust of the earth which resists degradation. Human get inflicted with heavy metals through the agency of food, water and atmosphere. Mercury poisoning by eating fishes is a prominent cause for public health hazard. Based on the review and analysis of physiological effects of different pharmaceutical chemicals and heavy metals, it was suggested that their indiscriminate and injudicious use produces anemia, leucopenia, hypoglycaemia, hypoproteinemia, increased enzymatic activity and hepatotoxic and nephrotoxic effects in broiler chickens.

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