Toxicological Effects of Carbofuran on the Water and Food intake in Albino Wistar Rat

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Citation

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Abstract

The effects of carbofuran on the water and food intake were undertaken. Furadan 3G (Carbofuran) a systematic N-methyl carbamate pesticide was orally administered at doses of 0.15, 0.1, and 0.05mg/kg body weight to normal male and female albino Wistar rat for eleven (11) weeks. The Dosing of albino Wistar rat was done every week for a period of eleven (11) Weeks. Water and food intake were measured daily for five (5) days prior to dosing and five (5) doses were also selected for analysis by the method adopted by Leonard et al., 2001. There was a significant ($p<.05$, $p<.02$, $p<.01$, $p<.001$) increase in water consumption for rats treated with 0.15, 0.1, and 0.05mg/kg carbofuran compared to control. Food consumption was shown to statistically significantly increase with 0.15mg/kg and decrease with 0.1, 0.05mg/kg carbofuran compared to control ($p<.05$, $p<.02$, $p<.01$, $p<.001$). These observed effects of carbofuran on water and food intake may be due to the effect of the pesticides on the hypothalamus likely via effects on the Paraventricular Nucleus (PVN) and Ventromedial Nucleus (VMN).

INTRODUCTION

Carbofuran® is a white crystalline solid with a slightly phenolic odour. It is a broad-spectrum insecticide, a pesticide and a nematicide and is sprayed directly onto soil and plants just after emergence to control beetles, nematode and rootworms. The greatest use of carbofuran® is on the following plants: Alfalfa, rice, with turf and grapes making up most of the remainder. The chemical was first introduced onto the market in 1965 (United States Environmental Protection Agency (EPA), (2004). Pesticides differ from any other chemical substances because they are deliberately spread into the environment. As a consequence, the great part of the human population may be exposed either in the general environment or in the working settings. The occupational exposure involving the manufacturing, and the use of pesticides, takes place mainly through dermal or respiratory route (Kaliwal et al., 2002) while the environmental exposure, involving the general population, is mainly due to the ingestion of the contaminated foods and water. Both the environmental and occupational exposure may not produce effects attributable to the pesticides at low doses (Kaliwal et al., 2002). Carbofuran (2, 3-dihydro-2, 2-dimethyl-7-benzofuranylmethylcarbamate), is a systemic N-methyl carbamate pesticide with predominantly contact (dermal-absorption through the intact skin) and stomach action (vomiting, nausea, abdominal cramp, diarrhea) (Kaliwal et al., 2002). It is mainly used as a soil applied chemical to control soil dwelling and foliar feeding insects and nematodes on a variety of agricultural crops, including maize, corn, rice, potatoes, alfalfa and grapes (Gupta, 1994). Carbofuran® is a potent cholinesterase inhibitor and is highly toxic to humans and wildlife through the oral and inhalation routes of exposure (Baron, 1991). A report showed that carbofuran is also used as an insecticide (see" Farm chemical handbook" 1986). In a two (2) year study, Charles River mice were fed dietary carbofuran concentration equivalent to 0, 2, 8, 18, 70mg/kg of body weight per day. Mice receiving the highest dose showed a decrease in body weight gain and a statistically significant depression of brain acetylcholinesterase (FAO/WHO, 1987). Furadan is the registered trade name for insecticidal formulations of carbofuran 2, 3-dihydro-2, 2-dimethyl-7-benzofuranylmethylcarbamate (Edward, et al., 1980). The name Furadan is used predominantly in the field, whereas carbofuran® (the common name) accepted by the American Standard Association has become the accepted name for the formulation used in the laboratory (Edward et al., 1980). The names Furadan and carbofuran® have been used interchangeably (Niagara Chemical Division, FMC Corporation, unpublished). Furadan 3G granular (3%

carbofuran® in a sand core granule) replaced aldrin in Texas in 1970 (Edward et al., 1980). In view of the above findings, the present study has been undertaken to attempt to characterize the effect of carbofuran® on the eating and drinking behavior of animals, specifically the laboratory rats.

MATERIALS AND METHODS

Technical grade Furadan 3G (carbofuran) was kindly provided by Mercy Agro Allied Company Ltd., located along Zaria – Samaru road and dissolved in distilled water as a vehicle for oral administration. Laboratory bred male and female albino rats weighing between 150 – 180g of both sexes were randomly selected from the animal house of the Department of Pharmacology, Ahmadu Bello University, Samaru, Zaria. All the animals were housed in separate Perspex cages (55cm x 33.5cm x 20cm) bedded with sawdust in a well ventilated laboratory at a temperature of approximately 33c and 12-12 hour light and dark cycle. Stable water and food intake baselines (less than 5% daily variation) were determined for all the study rats. The animals were observed for one week prior to the study. Only healthy animals were used for this study. The animals were fed on a mixture of commercial Pfizer chick mash (livestock feed, Lagos, Nigeria).The animals were given water ad libitum except when fasting was needed in the course of the study. Doses were given that ranged below the acute LD_{50} level of intoxication (Fahmy, et al., 1970). Animals were divided into 4 groups having 5 animals in each cage. Carbofuran administered in doses of 0.05, 0.1, 0.15mg/kg orally for 5 days. The controls group received equal volume of distilled water. The quantity of food eaten and water consumption were determined throughout the experiment.

DETERMINATION OF FOOD AND WATER INTAKE

Determination of food intake was carried out according to Leonard et al (2001). Drinking behavior after water deprivation is one of the standard tests used to study thirst in humans and animals and in addition, diurnal cycle, food availability are known to influence water intake (Leonard et al., 2001). In this experiment, adult male wistar rats were placed in four (4) separate Perspex cages and allowed to acclimatize to the laboratory environment for a week. During this period, water and food were given ad libitum. Pfizer chick mash was given to the rats throughout the experimental period. The animals were given three levels of doses. The oral route was used in this experiment. There were four groups of animals. The first group served as the control and animals were given distilled water. Group IV, III and II received 0.15, 0.1, 0.05mg/kg body weight of carbofuran respectively. Each group contained five (5) animals. The animals were given carbofuran® on a daily basis in addition to food and water. The animals were deprived of water for twenty four (24) hours. This was followed by feeding with water for 6 hours i.e. from 1 pm to 7pm the same day. Approximately one hundred milliliters (100mL) of water in the rat's feeding bottle was offered to the animal in each group. The animals were allowed free access to water for six (6) hours. After 6 hours, the final level of water was recorded. This was repeated for 5 times and the average taken. During this time the animals had free access to a measured amount of molded feed (chick mash) for thirteen (13) hours i.e. from 1pm to 2pm the following day. The cages were cleared of sawdust by the 13^{th} hour and the animals were deprived of food for 10hours. The experiment was repeated for five (5) times for both day and night. That is two nights and three days. The feed intake in grams were calculated thus; the feed intake in grams (g) eating/13 hours/100g rat were calculated as shown below

Food eaten (E) = Weight of feed given – weight of leftover feed.

Time interval (T) = 13 hours

Weight of animals/cage = K

Therefore, weight (g) of rats ate (E) feed in 13 hours

{image:1}

Similarly, the hundred milliliters (100ml) of water were offered to the rats in each cage for six hours (6 hrs). The rats had access to the water ad-libitum until they were removed at the 6^{th} hour after 24 hours of water deprivation. From the volume (ml) of water left undrinkable, the water intake in mls/rat/6 hours were calculated as shown below;

Water drank (B) = water given – water leftover.

Time interval (T) = 6 hours

Weight of animals/cage = J

Therefore, J (g) rats drank B (mls) of water in 6 hours.

{image:2}

Water consumed = Initial level of water in the cylinder – final level of water in the cylinder.

STATISTICS

Data were expressed as mean ± S.E.M from the observations. Student two tailed t-test for unpaired data or one way analysis of variance (ANOVA) for comparison among groups were used to determine the statistical significance of the difference between groups (Singha, 1996). $P < 0.05$, $P<0.02$, $P<0.01$, $P<0.001$ were considered to be significant.

RESULTS

WATER INTAKE

{image:3}

Administration of carbofuran® at doses of 0.05, 0.1, 0.15 mg/kg body weight to rats resulted in a significant ($P<0.05$, $P<0.02$, $P<0.01$) increase in water intake for 0.05, 0.1mg/kg and also a significant intake ($P<0.05$, $P<0.02$, $P<0.01$, $P<0.001$) for 0.15mg/kg compared to control (Table 1). The control rat exhibited normal drinking behavior as shown in figure 1.

{image:4}

FOOD INTAKE

{image:5}

Food consumption in rats administered 0.15mg/kg carbofuran® on a daily basis showed an increase in food consumption when compared to control, their difference was not significant ($P<0.05$) compared to control as seen in Fig 2; Table 2

At a reduced dose of 0.1mg/kg carbofuran® in group III showed a decrease in food consumption compared to control but the difference between the treated rats and control was not significant at $P<0.05$;Table 2

In group II, rats administered 0.05mg/kg carbofuran®, showed a decrease in weight of food consumed but was not significant compared to control ($P<0.05$); Table 2

{image:6}

Data were recorded as mean value of food consumed ±S.E.M.

DISCUSSION

In this study the toxicological effect of carbofuran on the water and food intake in laboratory rats were analyzed. A number of reports are available on the effect of carbofuran. We recently demonstrated in this study that albino Wistar rat administered 0.15, 0.1 and 0.05mg/kg carbofuran® does have a significant increase in food consumption compared to control. In order to examine the effect of carbofuran on the body weight of the albino Wistar rat it became necessary to also study how carbofuran influenced food and water intake. In this experiment, 0.05, 0.1 and 0.15mg/kg carbofuran® has a significant effect on food consumption compared with the control-there is an increase. However it has been reported that at higher dose of carbofuran® e.g. 100mg/kg, there were growth reduction and reduction in food consumption in mice treated with these doses of carbofuran® (Goldenthal, 1980; Brown, 1980). Similar report was given by Rapp (1980a). Prakash, et al., (2002) reported that there was a significant decrease in the body weight of rats in higher dose of carbofuran® treatment e.g. 100, 250mg/kg body weight as there may be suppression of food and water intake. In this present study, treatment of rat with 0.05, 0.1mg/kg carbofuran® showed a significant increase in water intake but at the 0.15mg/kg dose it showed a significance increase at in water consumption compared with the control. Several neuronal centres of the hypothalamus participate in the control of appetite. The lateral nuclei of the hypothalamus serve as the feeding centre, and stimulation of this area causes the animal to eat voraciously (hyperphagia), (Guyton and Hall, 2006). Conversely, destruction of the lateral hypothalamus causes lack of desire for food and progressive inanition, a condition characterized by weight loss, muscle weakness and decreased metabolism (Guyton and Hall, 2006). It was reported also that some environmental contaminants e.g. Carbofuran, endosulphan, influence motor and feeding behaviours in the ornate Wrasse (Thassoma pavo) via distinct cerebral histamine receptors subtypes (Giuseppina et al., 2005). It was further stressed that endosulphan markedly reduced feeding, even at a lower concentration. Endosulphan was noted to cause degeneration of interneurons of mammals (Siegel et al., 1999). Carbofuran like endosulphan acts similarly by (I) causing axonal deformations of interneurons in the hypothalamus, cellular alterations and interstitial infilterations in fresh water Teleost (Ram et al., 2001). Ram et al., (2001), also showed that such a contaminant could be responsible for a reduction in the number and size of neurons and consequently alter transmission function in the hypothalamus (II). Similarly, carbofuran also binds to histaminergic subtypes of receptors (H_1R, H_2R, and H3R) (Giuseppina et al., 2005). As was observed in the present study, there was a significant decrease in food consumption of the treated rats with 0.05, 0.1mg/kg carbofuran. This may have resulted from the

contamination of the neurons as reported by Giuseppina et al., (2005). The neuronal contamination (axonal deformation and alterations) leads to destruction of the nuclei in the lateral hypothalamus and consequently inhibition which present itself in the rats as reduced desire for food and inanition (Fig. 2). This was also characterized by weight loss as seen in the reduction in weight of rats compared with the control. Depression of brain acetylcholinesterase coupled with a decrease in body weight gain was also observed by FAO/WHO, (1987). The reduction in weight became more obvious in those rats treated with 0.1mg/kg carbofuran. With increasing dose, the ventral hypothalamus may also be involved in the destruction produced by carbofuran as observed by Ram et al., (2001). When the destruction occurs, the ventromedial nuclei of the hypothalamus that control satiety may be inhibited and the animal may show increased feeding reflected by a significant increase in food consumption compared with the control. This will again improve the weight of the animals over those animal exposed to lower dose of carbofuran e.g. 0.05, 0.1mg/kg carbofuran. The effect of pesticides (carbofuran, endosulphan), on histaminergic receptors subtypes of the hypothalamus reported by Giuseppina et al., (2005) was in line with the experiment of Fukagawa et al., (1989); Sakata et al., (1988), as quoted in this present work. It is also interesting to note that the histamine (HA) receptor complex is one of the main neuro-signaling systems that, in addition to "allergic" and anti-inflammatory processes, has been recognized for its role in many neurologic functions such as attention, arousal, cognition, movement, and feeding in mammalian species (Lin et al., 1996). Structurally, the histaminergic neuronal fibers, originating from the hypothalamus, are projected extensively throughout the central nervous system and promote their actions via three distinct receptor subtypes denoted H_nR (H_1R, H_2R, H_3R) (Hill et al., 1997). All but H_3R subtypes are located postsynaptically and are coupled positively to adenylyl cyclase and phospholipase C, whereas H_3R has been isolated at both the presynaptic and postsynaptic levels (Brown et al., 2001). Recently, Spieler et al., (1999) observed that inhibition of the H_1R site is linked to the improvement of appetitive reversal, learning and memory tasks in the goldfish Carassius auratus—a relationship that was further supported by the detection, via the application of their specific and selective antagonists, of H_3R (Peitsaro et al., 2000) and H_1R (Choich et al., 2004) in brain areas of the zebrafish Danio rerio and the tilapia Oreochromis niloticus, respectively. Moreover, identification of these subtypes in other vertebrates such as amphibians and reptiles (Brodin et al., 1990; Inagaki et al., 1991) is consistent with their highly conserved profile throughout vertebrate phylogeny (Kaslin and Panula, 2001). The reason for this could also be seen when the mechanism of action of carbofuran® and other organophosphates acting via inhibition of cholinesterase or as anticholinesterase were considered. McCann (1982) reported that wide varieties of pharmacologic agents that modify the neurotransmitter level would act at the level of the hypothalamus to adversely affect food and water intake. Recent studies showed that pesticides alter aggressive and reproductive behaviours in teleost fish (Carlson et al., 1988; Roex et al., 2001) through the interference of cerebral neuromediating systems (Clark, 1997) such as the histaminergic system. This system is actively involved in blocking chemical-dependent stressful conditions such as writhing and immobilization states (Ferretti et al., 1998; Ito, 2000). Sakata et al., (1988) established also the functional difference between Paraventricular nucleus (PVN) and Ventromedial nucleus (VMN) of the hypothalamus involved in drinking and eating behaviours in rats. Behavioural and electrophysiological findings suggest that neuronal histamine in the hypothalamus modulate feeding and drinking behaviours through H_1-receptors (Fukagawa et al., 1989). Palacios, et al., (1981) reported that the ventromedial hypothalamus (VMH) and Paraventricular nucleus (PVN) were known to be involved in this control and histaminergic pathways through these regions seem to be functionally different. For example, those through the histaminergic pathways in the VMH are involved in feeding modulation while those in the PVN mediate drinking behaviours (Sakata et al., 1988). Freeman (1993) observed dehydration and lacrimation in rats fed carbofuran. Although dehydration nor lacrimation were not directly measured in this experiment, there is no doubt dehydration may have played a crucial role towards increased consumption of water as seen with these rats. Acetylcholine pathways occur in the basal ganglia which include hypothalamus, caudate nucleus, putamen and so on (Guyton and Hall, 2006). It is interesting to note that there is a complex interrelationship between all the components of the basal ganglia (Obeso et al., 2004) of which hypothalamus is not an exception. Lessof (1986) reported that there is considerable similarity of structure among local hormones such as histamine and acetylcholine. This similarity in structure may bring about having similarity in the same mechanism of action as it relates acting in the same pathways. Since carbofuran® is a carbamate pesticide, an anti-cholinesterase, it would act at

the level of hypothalamus through the accumulation of acetylcholine to adversely affect food and water intake (Prakash, et al., 2002) as seen in significant increase in food intake at ($P<0.05$), ($P<0.02$), ($P<0.01$), ($P<0.001$). This may also have accounted for the gradual increase in body weight observed in the course of this experiment although less than that of the control. This was also seen in significant increase in water consumption with 0.05, 0.1 and 0.15mg/kg carbofuran. At this juncture, it is worthy of note that a compound that may block the action of one substance may also be capable of blocking the action of another (Laurence and Bennet, 1987). Apparently, some compounds that have anti-cholinergic properties may also have antihistaminic actions (Laurence and Bennet, 1987), hence the histaminergic pathways via the PVN and VMN of the hypothalamus may be influenced by acetylcholine. Reaction involving histamine may be similarly affected by reaction involving acetylcholine and vice versa (Laurence and Bennet, 1987). The brain anti-cholinesterase action of carbofuran is apparently enhanced in rats (Bloch et al., (1987a); FAO/WHO, (1987) leading to the accumulation of acetylcholine which may then influence the histaminergic pathways of the hypothalamus resulting in modification to feeding and drinking behaviour in rats. Thus the mechanism by which carbofuran regulate body weight may largely be due to their effect on food and water intake. Although there is no direct extrapolation of the effect of chemical to man from experiment on lower animal, there is great advantage as to know the toxicological profile of any chemical e.g. carbofuran® in this study, and hence knowledge of its safety at various dose level.

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