Toxicol. Int.Vol. 16, No. 2, 2009 pp 141-146

# Toxic effects of sub-chronic oral exposure of indoxacarb on biochemical parameters in buffalo calves

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## Abstract

**Repeated oral administration of Indoxacarb, an oxadiazine insecticide, at the dose rate of 1 mg/kg/day for 90 consecutive days produced mild signs of toxicity in buffalo calves. Indoxacarb significantly elevated the plasma levels of aspartate aminotransferase (38.3%), alanine aminotransferase (52.9%), alkaline phosphatase (29.5%) and acid phosphatase (36.6%). Cholinesterase levels in plasma, whole blood and erythrocyte also showed elevation. Indoxacarb did not produce any significant alterations in levels of blood urea nitrogen and creatinine. However there was an increase in blood glucose (16.9%), plasma cholesterol (19.6%) and total plasma proteins (10.8%). It can be concluded from the present study that indoxacarb is a low risk insecticide in buffalo calves.**

**Keywords**: Buffalo calves, indoxacarb, insecticides, sub-chronic toxicity.

## Introduction

Indoxacarb, (S)-methyl 7-chloro-2, 5-dihydro-2-[[(methoxycarbonyl) [4 (trifluoro methoxy) phenyl] amino]-carbonyl] indeno [1, 2-e] [1, 3, 4] oxadiazine-4a-(3H)-carboxylate, belongs to the new pesticide class oxadiazines. It is a pro-insecticide and undergoes bioactivation to the N-decarbomethoxylated metabolite (Wing *et al.*, 1998), which is much more toxic than the parent compound. The activated metabolite of indoxacarb has a unique mode of action involving the blocking of sodium channels of nerve cells, resulting in paralysis and death of the target pest species (Dinter and Wiles 2000, Lapied *et al.,* 2001). Some results indicated that the oxadiazine insecticide has potent modulating actions on neuronal nicotinic AChRs. The neuronal nicotinic AChR could be one of the primary target sites of the insecticide in mammals (Zhao *et al.,* 1999).

Indoxacarb is mainly used in agriculture and horticulture and exhibits strong activity against lepidopteran pests of vegetables, tree fruits, cotton, corn, peanut, soybean, alfalfa and other crops (Harder *et al.*, 1997). Activity of this compound has also been shown against some homopteran and coleopteran species (Wing *et al.*, 2000). The animals are likely to come in contact with this insecticide from the recently applied fields, through its residues in feed and fodder, or when insecticide is applied directly to water bodies. Run off from treated areas may also be hazardous to aquatic organism in neighbouring areas. (National Registration Authority for Agricultural and Veterinary Chemicals, 2000). The present study was, therefore, planned to study the effect of repeated oral administration of sub-chronic doses of indoxacarb on various clinical and biochemical parameters in buffalo calves.

## Materials and Methods

Seven healthy male buffalo calves aging 9-12 months and weighing between 56-85 kg were used. The animals were maintained on seasonal green fodder and water was provided *ad libitum*. Prior to the experiment, deworming of the animals was ensured using Albendazole. Blood samples were collected for determining the normal values of various biochemical parameters. The animals were randomly divided into two groups of 3 and 4 animals each, Group1 served as control to which no insecticide was administered. The animals in Group II were administered indoxacarb in repeated oral dose of 1 mg/kg/day for 90 consecutive days. All animals were

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weighed weekly and doses of indoxacarb corrected according to change in body weight.

Blood was collected in heparin containing test tubes on weekly basis by jugular vein puncture to study the biochemical parameters. For estimation of glucose, blood was collected without anticoagulant (Frankel *et al*., 1970). Plasma enzymes, aspartate animotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and acid phosphatase (ACP) were estimated using the standard methods of Wootton (1964). Plasma, erythrocyte and whole blood cholinesterase activities were measured according to the method of Voss and Sachsse (1970) as modified by Moroi *et al*. (1976). Blood urea nitrogen (BUN), plasma creatinine and plasma cholesterol levels were determined by the method of Wootton (1964). Total Proteins were determined by method of Reinhold (1953). Statistical analysis of the data was performed by applying student's't' test (Snedecor and Cochran, 1967).

## Results and Discussion

Daily oral administration of indoxacarb at dose rate of 1mg/kg/day produced mild toxicosis in buffalo calves. Indoxacarb produced signs of decrease in body weight, lameness, decrease feed intake and nasal discharge. Although there are no reports available on pharmacological or toxicological studies of oxadiazine insecticide in buffalo calves to substantiate the above findings, but findings of Wing *et al*. (2000) suggested that neurotoxic symptoms due to toxicants often lead to a rapid cessation of feeding. Indoxacarb at a dose rate of 1 mg/kg/day for 90 consecutive days produced significant increase in plasma aspartate aminotransferase (38.3%) and alanine aminotransferase activity (52.9%). Activity of AST is usually high in acute and chronic liver injury (Tennant, 1997) and muscular damage (Brar *et al.,* 2000). Alanine aminotransferase is employed as a marker of hepatocellular damage and in general is considered a more sensitive indicator of liver cell injury than AST (Cohn and Kaplan, 1971; Oser, 1976). Though AST and ALT are not known to have any function in the plasma, yet their increased levels in blood indicate cellular damage, increase membrane permeability (Ramazzotto and Carlin, 1978) and their altered metabolism (Dinman *et al.,* 1963). Although it is difficult to suggest the damage to any particular organ by indoxacarb, but increased levels of aminotransferase in ruminants is attributed to liver damage (Cornelius, 1989), as it is the primary organ of biotransformation of insecticides.

Repeated oral administration of indoxacarb @ 1mg/kg/day produced elevation in plasma alkaline phosphatase (29.5%) and acid phosphatase (36.6%) activities on 90$^{th}$ day of experiment (Table1). It has been reported that any damage to liver, bone, small intestine and kidney may liberate alkaline phosphatase in blood stream (Kaplan and Righetti, 1970). On the other hand, acid phosphatase is a lysosomal enzyme that gets stimulated in cases of imminent or prevalent tissue damage (Wilson *et al.,* 1970) or release of phosphatase occurs due to its increased synthesis brought about by variety of liver conditions (Seetharam *et al.,* 1986). After repeated oral administration of 1 mg/kg/day indoxacarb for 90 consecutive days in buffalo calves there was 11.8% elevation in plasma cholinesterase levels, 21.9% elevation in erythrocyte cholinesterase level and 13.8 % elevation in whole blood cholinesterase levels (Table 2), which suggested that indoxacarb has slight effect on neurological system (Zlotkin, 2001).

Sub-chronic oral exposure of indoxacarb did not produce any significant alterations in levels of blood urea nitrogen and creatinine. The results indicated that indoxacarb did not adversely affect the renal functions. There were elevations in levels of blood glucose (16.9%), plasma cholesterol (19.6%) and total plasma proteins (10.8%) in buffalo calves following repeated oral administration of indoxacarb (1mg/kg/day) for 90 consecutive days (Table 3). The studies indicated that there was dose-dependent hyperglycemia and stress to the animal. Welch (1993) documented that exposure to any environmental stress increase the production of stress proteins in the body. Alterations in cholesterol levels are not liver specific but elevated level of total cholesterol and its ester can be observed in domestic animal having biliary obstruction (Cornelius, 1989).

**Table 1: Effect of sub-chronic oral administration of indoxacarb (1 mg/kg/day) on plasma aminotransferases and phosphatases in buffalo calves.**

| | Time (Weeks)Treatment | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| **Aspartate aminotransferase (nmol pyruvate formed/min/ml)** | | | | | | | | | | | | | | |
| Control[a] | 57.6 ±3.63 | 59.3 ±4.03 | 57.2 ±3.54 | 60.1 ±5.35 | 58.5 ±5.23 | 60.0 ±4.83 | 57.2 ±3.71 | 58.0 ±3.69 | 59.7 ±4.68 | 60.6 ±3.48 | 62.0 ±2.54 | 61.2 ±3.12 | 61.5 ±4.31 | 60.9 ±4.20 |
| Indoxacarb | 60.0 ±4.23 | 60.6 ±6.16 | 61.7 ±3.65 | 63.5 ±4.37 | 66.3 ±5.11 | 67.5 ±5.18 | 70.4 ±4.84 | 69.2 ±4.62 | 71.0 ±2.35 | 72.8 ±5.26 | 75.6 ±2.52** | 78.2 ±2.19** | 81.3 ±2.72** | 83.0 ±2.50** |
| **Alanine aminotransferase (nmol pyruvate formed/min/ml)** | | | | | | | | | | | | | | |
| Control[a] | 37.0 ±2.74 | 37.0 ±2.22 | 39.7 ±4.23 | 36.3 ±4.35 | 37.9 ±3.35 | 40.5 ±2.50 | 38.7 ±3.89 | 38.9 ±2.72 | 40.2 ±2.66 | 38.7 ±3.15 | 37.0 ±3.49 | 38.0 ±2.50 | 36.4 ±3.94 | 39.2 ±3.83 |
| Indoxacarb | 39.0 ±3.44 | 39.3 ±3.48 | 42.7 ±3.61 | 37.3 ±3.47 | 41.5 ±2.95 | 45.8 ±4.35 | 47.3 ±4.17 | 48.7 ±5.91 | 51.4 ±3.49 | 53.8 ±4.23* | 51.5 ±4.52 | 57.7 ±4.19** | 61.9 ±5.37** | 63.5 ±3.26** |
| **Alkaline phosphatase (nmol phenol liberated/min/ml)** | | | | | | | | | | | | | | |
| Control[a] | 59.3 ±2.73 | 69.9 ±2.52 | 69.1 ±1.96 | 66.1 ±2.26 | 68.0 ±2.54 | 70.4 ±2.14 | 69.1 ±3.23 | 68.3 ±2.60 | 68.6 ±3.00 | 69.3 ±1.67 | 68.4 ±2.25 | 68.6 ±1.72 | 66.7 ±1.66 | 69.1 ±1.52 |
| Indoxacarb | 67.7 ±1.83 | 68.3 ±2.25 | 70.3 ±2.40 | 71.8 ±1.97 | 72.3 ±1.76 | 70.4 ±1.98 | 72.9 ±1.37 | 73.5 ±1.52 | 74.2 ±1.66 | 76.2 ±2.06** | 78.3 ±1.44** | 76.8 ±2.01* | 82.0 ±2.36** | 87.6 ±2.25** |
| **Acid phosphatase (nmol phenol liberated/min/ml)** | | | | | | | | | | | | | | |
| Control[a] | 1.76 ±0.06 | 1.79 ±0.04 | 1.71 ±0.08 | 1.81 ±0.03 | 1.74 ±0.09 | 1.76 ±0.10 | 1.80 ±0.09 | 1.76 ±0.12 | 1.80 ±0.08 | 1.83 ±0.08 | 1.77 ±0.13 | 1.83 ±0.06 | 1.72 ±0.14 | 1.76 ±0.05 |
| Indoxacarb | 1.83 ±0.07 | 1.88 ±0.08 | 1.82 ±0.06 | 1.93 ±0.04 | 1.97 ±0.03 | 2.00 ±0.07 | 2.04 ±0.14 | 2.07 ±0.12 | 2.10 ±0.07 | 2.18 ±0.15 | 2.22 ±0.10* | 2.30 ±0.16** | 2.41 ±0.08 | 2.50 ±0.09** |

The values are mean ± SE of 4 animals, unless otherwise stated; a= values are mean ± SE of 3 animals; * $P<0.05$; ** $P<0.01$

**Table 2: Effect of subchronic oral administration of indoxacarb (1mg/kg)/day on plasma, erythrocyte and whole blood cholinesterase activity in buffalo calves.**

| | Time (Weeks)Treatment | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| **Plasma cholinesterase (nmol acetylthiocholine hydrolyzed/min/ml)** | | | | | | | | | | | | | | |
| Control[a] | 157.4 ±5.27 | 158.9 ±6.58 | 154.8 ±11.3 | 151.5 ±6.49 | 165.2 ±8.10 | 173.1 ±4.96 | 158.6 ±4.95 | 166.6 ±8.62 | 160.4 ±4.12 | 156.5 ±4.28 | 169.4 ±14.4 | 156.9 ±1.45 | 159.6 ±1.88 | 162.9 ±1.06 |
| Indoxacarb | 161.3 ±4.46 | 164.3 ±4.72 | 160.9 ±4.10 | 161.9 ±7.11 | 167.8 ±3.27 | 159.2 ±10.9 | 164.7 ±1.54 | 174.9 ±5.31 | 168.4 ±4.16 | 164.2 ±3.64 | 172.3 ±7.90 | 176.0 ±4.10** | 177.0 ±2.92** | 179.4 ±6.32** |
| **Erythrocyte cholinesterase (nmol acetylthiocholine hydrolyzed/min/ml)** | | | | | | | | | | | | | | |
| Control[a] | 1953.1 ±115.4 | 1951.2 ±98.4 | 1857.3 ±182.2 | 1938.0 ±120.3 | 1946.9 ±130.5 | 1959.0 ±142.4 | 1909.2 ±117.3 | 1919.2 ±101.2 | 1910.4 ±135.7 | 1933.0 ±103.2 | 1919.0 ±182.3 | 1964.9 ±103.5 | 1980.4 ±101.2 | 1955.7 ±98.0 |
| Indoxacarb | 2024.6 ±207.2 | 2096.8 ±135.3 | 1980.8 ±156.8 | 2002.9 ±179.5 | 2057.1 ±167.2 | 2103.8 ±125.9 | 2127.7 ±147.8 | 2163.1 ±126.2 | 2150.1 ±106.1 | 2265.0 ±111.9 | 2308.7 ±98.7* | 2375.4 ±92.5* | 2418.3 ±94.2* | 2468.9 ±115.9* |
| **Whole blood cholinesterase (nmol acetylthiocholine hydrolyzed/min/ml)** | | | | | | | | | | | | | | |
| Control[a] | 568.6 ±25.6 | 577.4 ±20.2 | 553.8 ±31.1 | 567.3 ±19.3 | 573.5 ±30.1 | 561.5 ±21.3 | 565.9 ±34.0 | 562.9 ±22.8 | 569.8 ±18.5 | 573.6 ±29.7 | 562.2 ±15.0 | 554.3 ±21.5 | 566.9 ±40.3 | 563.9 ±31.8 |
| Indoxacarb | 624.1 ±24.0 | 644.0 ±15.9 | 607.3 ±21.7 | 617.3 ±27.1 | 623.1 ±17.9 | 635.9 ±25.9 | 653.1 ±40.1 | 664.5 ±32.9 | 651.1 ±35.2 | 675.3 ±26.7 | 687.8 ±20.3* | 692.9 ±40.3* | 700.7 ±24.9* | 710.5 ±32.2* |

The values are mean ± SE of 4 animals, unless otherwise stated
a= values are mean ± SE of 3 animals.
* $P<0.05$ ** $P<0.01$

**Table 3: Effect of subchronic oral administration of indoxacarb (1mg/kg/day) on total serum proteins, blood urea nitrogen, plasma creatinine, blood glucose and plasma cholesterol in buffalo calves.**

| Time (Weeks)Treatment | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Total Plasma Proteins (g/dl)** | | | | | | | | | | | | | | |
| Control[a] | 5.6 ±0.11 | 5.48 ±0.12 | 5.51 ±0.10 | 5.40 ±0.08 | 5.59 ±0.06 | 5.52 ±0.09 | 5.51 ±0.12 | 5.55 ±0.08 | 5.64 ±0.11 | 5.58 ±0.12 | 5.60 ±0.10 | 5.53 ±0.12 | 5.69 ±0.09 | 5.66 ±0.12 |
| Indoxacarb | 5.66 ±0.13 | 5.65 ±0.08 | 5.71 ±0.12 | 5.72 ±0.11 | 5.74 ±0.16 | 5.76 ±0.08 | 5.83 ±0.11 | 5.87 ±0.12 | 6.00 ±0.09** | 6.02 ±0.14 | 6.10 ±0.16 | 6.16 ±0.14* | 6.22 ±0.17* | 6.27 ±0.14* |
| **Blood Urea Nitrogen(mg/dl)** | | | | | | | | | | | | | | |
| Control[a] | 3.27 ±0.33 | 3.32 ±0.69 | 3.17 ±1.02 | 3.63 ±0.78 | 3.33 ±0.54 | 3.94 ±0.63 | 3.72 ±0.16 | 3.48 ±0.32 | 3.36 ±0.31 | 3.34 ±0.28 | 3.35 ±0.32 | 3.62 ±0.37 | 3.70 ±0.19 | 3.55 ±0.41 |
| Indoxacarb | 3.46 ±0.26 | 3.42 ±0.32 | 3.40 ±0.26 | 3.17 ±0.42 | 3.23 ±0.32 | 3.22 ±0.28 | 3.58 ±0.41 | 3.55 ±0.44 | 3.52 ±0.38 | 3.60 ±0.29 | 3.55 ±0.33 | 3.63 ±0.39 | 3.49 ±0.27 | 3.60 ±0.12 |
| **Blood Glucose(mg/dl)** | | | | | | | | | | | | | | |
| Control[a] | 54.2 ±4.32 | 55.7 ±4.04 | 54.8 ±2.18 | 55.3 ±2.64 | 56.5 ±1.48 | 56.9 ±2.94 | 54.4 ±2.13 | 53.2 ±2.97 | 58.3 ±2.38 | 55.7 ±1.78 | 56.7 ±1.69 | 55.6 ±1.97 | 58.9 ±1.20 | 56.7 ±1.19 |
| Indoxacarb | 58.8 ±1.23 | 58.8 ±2.25 | 59.1 ±1.83 | 59.2 ±3.25 | 60.7 ±2.78 | 61.1 ±1.28 | 62.1 ±2.47 | 62.8 ±2.36 | 63.9 ±1.69 | 64.9 ±1.86* | 65.3 ±2.47* | 67.1 ±1.94** | 68.6 ±1.36** | 68.7 ±2.63** |
| **Plasma Creatinine(mg/dl)** | | | | | | | | | | | | | | |
| Control[a] | 1.13 ±0.08 | 1.14 ±0.17 | 1.25 ±0.05 | 1.11 ±0.06 | 1.17 ±0.04 | 1.15 ±0.07 | 1.26 ±0.20 | 1.15 ±0.06 | 1.18 ±0.08 | 1.18 ±0.12 | 1.26 ±0.14 | 1.11 ±0.13 | 1.14 ±0.10 | 1.24 ±0.09 |
| Indoxacarb | 1.26 ±0.07 | 1.31 ±0.10 | 1.34 ±0.04 | 1.38 ±0.15 | 1.32 ±0.16 | 1.40 ±0.13 | 1.49 ±0.03 | 1.45 ±0.14 | 1.54 ±0.12 | 1.58 ±0.11 | 1.54 ±0.08 | 1.51 ±0.09 | 1.45 ±0.07 | 1.49 ±0.14 |
| **Plasma Cholesterol(mg/dl)** | | | | | | | | | | | | | | |
| Control[a] | 100.3 ±6.23 | 108.4 ±7.41 | 104.5 ±5.98 | 105.6 ±5.95 | 109.3 ±7.50 | 110.2 ±7.72 | 105.7 ±9.99 | 106.4 ±8.71 | 110.4 ±9.89 | 116.6 ±7.01 | 114.0 ±9.44 | 107.7 ±9.49 | 110.4 ±6.27 | 115.8 ±7.86 |
| Indoxacarb | 121.0 ±8.29 | 123.3 ±9.36 | 122.4 ±9.83 | 125.3 ±8.89 | 131.2 ±8.26 | 137.3 ±8.45 | 136.6 ±9.11 | 139.8 ±10.1 | 141.8 ±8.10 | 142.3 ±8.56 | 141.7 ±8.92 | 143.3 ±9.91 | 142.5 ±8.82* | 144.7 ±8.06 |

The values are mean ± SE of 4 animals, unless otherwise stated; a= values are mean ± SE of 3 animals; * P<0.05; ** P<0.01

It can be concluded from the present study that indoxacarb is mildly toxic to buffalo calves when administered in repeated oral doses of 1mg/kg/day for 90 consecutive days. The biochemical studies suggested that indoxacarb is a low risk insecticide in buffalo calves.

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*Received : 27.12.2008*
*Accepted: 05.02.2009*