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Salinomycin Toxicity in Chickens: Biochemical Changes and Treatment with Hypertonic Dextrose

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Abstract: Salinomycin is a monocarboxylic polyether antibiotic with antimicrobial properties. It is used as a coccidiostat in chickens and a growth promoter in ruminants. Although it has proved to be safe at therapeutic doses, a toxic effect can result from overdosage or misuse. Thus, changes in biochemical parameters (AST, ALT and CK) were examined and the effect of hypertonic (50%) dextrose against experimental toxicosis with salinomycin was evaluated in broiler chickens (male and female) and laying hens in this study. Male and female broilers and laying hens each were divided into 6 groups (n=9). Except for group 1, all birds were intoxicated with oral administration of salinomycin (85 mg kg^{-1}). Group 2 received intravenous saline (1 ml kg^{-1}) 1 hour after poisoning. Hypertonic dextrose (1 or 2 ml kg^{-1}, either single or double doses) was similarly injected into the wing vein of the chickens in groups 3 to 6. The number of deaths after salinomycin poisoning was recorded for each group. Blood samples were collected from the wing vein on days 0, 3, 7 and 14. Results indicate that mortalities decreased in those groups receiving dextrose solution, particularly in group 6, compared to the mortality in group 2. In male and female broilers, hypertonic dextrose decreased the mortalities up to 22%, but about 44% in laying hens. AST, ALT and CK levels in serum increased in those groups intoxicated with salinomycin, however, after the administration of dextrose the situation was reversed and the levels of enzymes in the serum mostly decreased in various groups. It is generally concluded that the administration of hypertonic dextrose is partially useful in the treatment of salinomycin toxicosis in the chicken. The mechanism by which dextrose exerts this effect should be investigated in future studies.

Key words: Salinomycin toxicity, biochemical parameters, hypertonic dextrose, chickens

INTRODUCTION

Carboxylic ionophores are a group of polyether antibiotics comprised of many different compounds (Callaway et al., 2003; Butaye et al., 2003). Monensin, lasalosid, narasin, maduramicin and salinomycin are some members of this group (Maas et al., 2001). These antibiotics are characterized by multiple tetrahydrofuran and tetrahydropyran rings connected by aliphatic bridges. Other important features also contributing to their mode of action include a free carboxyl function (EFSA, 2008).

Ionophores are widely used as an anticoccidial drug for poultry and as a growth promoter for ruminants (Anderson et al., 1984; Nagaraja et al., 1996; Kinashi et al., 1973; Wilson, 1980). Generally, ionophores have been shown to be safe and effective in target animals receiving recommended dosage concentrations. However, overdosage or misuse situations can lead to toxic syndromes (Wilson, 1980; Galitzer et al., 1982; Schweitzer et al., 1984; Novilla, 1992; Rajaian et al., 2008).

Salinomycin is a member of ionophores produced by the fermentation of the fungal stereptomyces species which is active against some Gram positive bacteria, coccidia, neospora and toxoplasma (Mckellar and Lawrence, 1980). It has a narrow therapeutic index and is toxic to turkey and mammals at relatively low dose (Todd et al., 1984).

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Chickens are relatively resistant to ionophore poisoning compared to other species (Gregory, 1997). One reason could be the extent of the metabolism of ionophores occurring in this species (Nebbia et al., 2001).

The mechanism of action of ionophores at the cellular level is to selective binding, with certain ions creating intra and extra cellular biochemical disturbance. Salinomycin preferentially binds with potassium, interfering with potassium transport across mitochondrial membranes and resulting in low intra cellular energy production.

So far, no antidote or proven treatment regimen has been introduced for ionophore toxicosis (Jones, 2001). The use of emetics (in small animal only) and activated charcoal or mineral oil in combination with saline cathartics, may decrease the absorption of ionophore drugs (Haward, 1993). Compensation for the energy depletion may be useful to alleviate the toxic effects of salinomycin. Therefore, the effectiveness of hypertonic (50%) dextrose (HD) against salinomycin toxicosis in male and female broilers and laying hens was examined in the present study. In addition, changes in several biochemical parameters (AST, ALT and CK) were also evaluated.

MATERIALS AND METHODS

Male and female broiler chickens (6 week old Hi- line breed, weighing 1500-2250 g) and laying hens (44 week old Ross breed, weighing 1350-2050 g) were used in accordance with the international guiding principles involving animals for scientific researches as well as the guidelines of animal welfare. Layer hens and broiler chickens were each randomly divided into six groups (n=9) as follows:

Group 1: not intoxicated with salinomycin and received no treatment.
Group 2: intoxicated with salinomycin and received isotonic saline.
Group 3: intoxicated with salinomycin and received a single dose (1ml kg^{-1}) of HD.
Group 4: intoxicated with salinomycin and received a double dose (1ml kg^{-1}) of HD.
Group 5: intoxicated with salinomycin and received a single dose (2ml kg^{-1}) of HD.
Group 6: intoxicated with salinomycin and received a double dose (2ml kg^{-1}) of HD.

The first dose was injected one hour after the administration of salinomycin and the second dose was administered 24 hours after salinomycin poisoning. A proper dose of salinomycin was selected on the basis of a series of experiments leading to the determination of LD_{50} of the ionophore in various birds using up and down dosing (Neuschl et al., 2001; Vaczi et al., 2006; Rajaian et al., 2009). The effect of treatment with HD on the death rate was then examined following the oral administration of salinomycin (85 mg kg^{-1}). Mortalities in the various groups were statistically compared using the Qui-Square test.

Blood samples were collected from the wing veins of the chickens at different time intervals (0, 3, 7 and 14 days after the administration of salinomycin) and several biochemical parameters (AST, ALT and CK) were measured using a standard autoanayser with veterinary software (Bayer, Model 560, Germany). Data were analyzed by univariant analysis of variance and Tukey HSD.

RESULTS AND DISCUSSION

The LD_{50} of salinomycin in broiler chickens and laying hens was determined to be around 106 and 104 (mg kg^{-1}), respectively. The effects of the treatment with HD on the rate of mortality, following the oral administration of salinomycin (85 mg kg^{-1}), are shown in Table 1.

A lower death rate was observed in broilers (both sexes) and laying hens compared to the group not receiving HD therapy. Birds in the control group (not intoxicated with salinomycin, group 1) showed no mortality. A similar situation was noticed in group 6 in broilers (both sexes). In male broiler chickens the percentages of death in groups 2, 3 and 5 were around 33, 11 and 11, respectively, but no death has occurred in group 4. In female broiler chickens, the approximate percentages of mortalities in groups 2, 3, 4, and 5 were 44, 33, 33 and 22, respectively. In laying hens, however, the percentages of death in groups 2, 3, 4, 5 and 6 were around 44, 11, 22, 11 and 11, respectively.

Generally, there was no mortality in the control group not intoxicated with salinomycin. The rate of mortality in the intoxicated group not receiving HD therapy was around 40%. This is in accordance with our expectation, as a dose smaller than LD_{50} has been administered to chickens. On the other hand, the rate of mortality was decreased to at least 4% in groups treated with HD (Table 1).

Values of serum AST, ALT and CK in different groups of broiler chickens and laying hens are depicted in Tables 2, 3 and 4. The enzyme activities of AST and ALT significantly ($P<0.05$) increased following the administration of salinomycin in the chickens (Tables 2 and 3). Although apparently significant differences exist between the groups in several cases, generally there were no major changes in the serum AST level on day zero. However, from day 3, the enzyme level in the serum increased 2 to 5 fold in most groups compared to the control group (group 1) and did not return to the normal level, even 2 weeks after salinomycin intoxication (Table 2). The situation for the serum ALT level was more or less similar to that for the serum AST. The discrepancies in the data obtained for ALT seem to be higher than those shown for AST (Tables 3 and 2).

The activity of CK was elevated more than ten-fold compared to the control group on day 3 and then started to decrease in the following days (Table 4). In contrast to the gradual increase in the serum AST and ALT levels, the ionophore exerted a sharp increase in the serum CK levels in almost all groups. In addition, the CK levels in those groups treated with HD declined relative to the non-treated control group (Table 4).

Table 1: Number of mortalities of chickens after oral administration of salinomycin (85 mg kg^{-1}) in various groups of birds

Groups			Treated with HD[2]			
			1 ml kg^{-1}		2 ml kg^{-1}	
Birds	Control (G1)[1]	Saline (G2)	Single dose(G3)	Double dose (G4)	Single dose (G5)	Double dose (G6)
Male broilers	No death	3 out of 9	1 out of 9	No death	1 out of 9	No death
Female broilers	No death	4 out of 9	3 out of 9	2 out of 9	2 out of 9	No death
Laying hens	No death	4 out of 9	1 out of 9	2 out of 9	1 out of 9	1 out of 9
Total	No death	11 out of 27 (40)[3]	5 out of 27*(18)	4 out of 27*(15)	4 out of 27*(15)	1 out of 27*(4)

[1]G1: not intoxicated with salinomycin and no treatment
G2: intoxicated with salinomycin and received isotonic saline.
G3: intoxicated with salinomycin and received a single dose (1ml kg^{-1}) of HD.
G4: intoxicated with salinomycin and received a double dose (1ml kg^{-1}) of HD.
G5: intoxicated with salinomycin and received a single dose (2ml kg^{-1}) of HD.
G6: intoxicated with salinomycin and received a double dose (2ml kg^{-1}) of HD.
[2]Hypertonic dextrose (50%)
[3]Approximate percentage
*Significant ($P<0.05$) difference compared with the group that received saline.

Table 2: Activity of AST in chickens after oral administration of salinomycin (85 mg kg^{-1}) in various groups of birds

Time	Bird	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Day 0	Broiler male	386± 106 aAI	362± 111aAI	225± 9bAI	219± 17bAI	214.7± 8.9bAI	220± 9bAI
	Broiler female	324± 118aAII	220± 21aBII	236± 23aAII	256± 26bAII	244± 33aAII	225± 37aAII
	Layer	191± 12aBIII	209± 21aBIII	203± 31aAIII	234± 19aAIII	164± 9bBIII	241± 27bAIII
Day 3	Broiler male	203± 19aAII	1845± 970bAI	311± 55cAII	715± 96cAII	475± 93cAII	594± 101cAII
	Broiler female	203± 17aAII	710± 81bAII	858± 147bBI	692± 95bAI	631± 98bAI	620± 132bAI
	Layer	197± 22aAIII	673± 106bAI	346± 61cAII	790± 94bAI	543± 88bAI	563± 112bAI
Day 7	Broiler male	199± 19aAII	986± 106bAII	860± 143bAIII	868± 171bAII	450± 73cAII	698± 146cAII
	Broiler female	195± 14aAII	674± 56bBI	789± 155bAI	797± 25bAI	474± 83cAI	723± 229bAI
	Layer	197± 22aAIII	1013± 92bAII	843 ±134.bAIII	595± 150cBI	645± 161cAI	860± 184bAII
Day 14	Broiler male	270± 64aAI	893± 93bAII	855± 136bAIII	450± 110cAIII	698± 123bAIII	1083± 167bAIII
	Broiler female	194± 40aAII	808± 84bAI	933± 140bAI	767± 59bBI	325± 43cBIII	755± 165bAI
	Layer	197± 22aAIII	984± 116bAII	972± 124bAIII	536± 87cAI	753± 151bAI	771± 198bAII

Number of birds=3-9; Different letters indicate significant ($p<0.05$); Large letters compared groups in rows; Large letters compared groups in columns for various birds on a specific day; Italic number compared broiler male, broiler female and layers in columns on various days.

Table 3: Activity of ALT in chickens after oral administration of salinomycin (85 mg kg^{-1}) in various groups of birds

Time	Bird	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Day 0	Broiler male	5.2± 1.6aAI	5.2± 1.2aAI	3.3± 0.7aAI	4.7± 1.1aAI	3.1± 0.6aAI	5.2± 1.9aAI
	Broiler female	6.7± 3.5aAII	3.7± 0.5aAII	4.4± 1.0aAII	6.1± 2.4aAII	3.2± 0.5aAII	4.0± 0.8aAII
	Layer	3.4± 0.3aAIII	3.7± 0.4aAIII	2.9± 0.4aAIII	3.4± 0.8aAIII	3.2± 0.9aAIII	3.9± 0.6aAIII
Day 3	Broiler male	3.4± 0.6aAI	11.7± 1.3bAII	6.5± 1.5cAII	14.7± 1.1cAII	6.6± 0.9cAII	9.9± 1.5bAII
	Broiler female	3.7± 0.5aAII	12.8± 0.4bAI	11.6± 1.8bBI	13.5± 0.6bI	7.8± 0.4cAI	7.6± 2.0cAI
	Layer	2.6± 0.4aABI	11.7± 1.3bAI	6.8± 1.4cBI	14.8± 0.7cAI	7.4± 0.6cAI	7.8± 1.7cAI
Day 7	Broiler male	4.4± 0.7aAI	15.5± 1.1bAIII	12.5± 2.3bAIII	12.2± 3.0cAII	7.4± 1.7cAII	9.6± 2.2cAII
	Broiler female	2.9± 0.5aBII	13.7± 0.3bBIII	14.2± 1.9bAI	15± 0.8bIII	9.3± 0.6cAIII	8.5± 2.4cAI
	Layer	2.6± 0.3aBI	13.4± 1.5bABI	12.4± 0.1bAII	11.7± 1.5bAII	10.8± 1.3bABII	8.3± 1.3cAI
Day 14	Broiler male	7.4± 1.6aAI	15.7± 1.5bAIII	15.7± 2.6bAIII	12.0± 3.2bAII	14.9± 3.4bAIII	18.3± 1.9bAIII
	Broiler female	7.4± 1.6aAII	15.7± 1.5bBI	15.7± 2.6bAI	12.0± 3.2cAIII	14.9± 3.4cBIII	18.3± 1.9bAI
	Layer	2.6± 0.3aBI	13.5± 1.5bABI	13.3± 0.8bAI	11.7± 1.8bABII	11.5± 1.2bAII	8.5± 1.6cAI

Number of birds=3-9; Different letters indicate significant ($p<0.05$); small letters compared groups in rows; Large letters compared groups in columns for various birds on a specific day; Italic number compared broiler male, broiler female and layers in columns on various days.

Table 4: Activity of CK in chickens after oral administration of salinomycin (85 mg kg^{-1}) in various groups of birds

Time	Bird	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Day 0	Broiler male	3881± 655aAI	4244± 533aAI	4201± 618aAI	3647± 878aAI	5587± 484bAI	4775± 190aAI
	Broiler female	3881± 655aAII	4244± 533aBII	4201± 618aBII	3647± 878aAII	5587± 484aAII	4775± 190aBII
	Layer	4525± 647aBIII	4652± 759aAIII	4203± 627aAIII	5121± 656aAIII	1937± 203bBIII	5591± 793aBIII
Day 3	Broiler male	2660± 359aAII	46095± 651bAII	43750± 501cAII	41036± 412cAII	38285± 213cAII	36860± 161cAII
	Broiler female	3102± 264aAII	45232± 33bBI	42782± 590cAI	40661± 339cAI	38330± 326cI	36366± 329cBI
	Layer	3482± 543aAIII	46715± 948bAI	42745± 452cAI	40966± 97cAI	37998± 362AcAI	29126± 7059cBI
Day 7	Broiler male	4449± 1206AaI	40868± 282bAIII	38137± 305cAIII	35262± 388cAIII	31717± 418cAIII	28998± 353cAIII
	Broiler female	3517± 298aAII	41349± 261bAIII	38155± 104cAIII	35077± 187cAIII	31453± 212cAIII	29173± 206cAIII
	Layer	3482± 543aAIII	41534± 371bAII	37994± 113cAII	35024± 229cAII	32116± 359cAII	28874± 240cAII
Day 14	Broiler male	4279± 684aAI	31064± 173bAIV	27976± 186cAIV	24221± 374cAIV	21527± 223cAIV	18368± 237cAIV
	Broiler female	4071± 1109aAII	30930± 423bAIV	27681± 450cAIV	23879± 185cAIV	21078± 68cAIV	17960± 306cAIV
	Layer	3482± 543aAIII	31284± 244bAIV	26841± 175cBIV	23955± 271cAIV	20872± 343cAIV	18275± 330cAIV

Number of birds=3-9; Different letters indicate significant ($p<0.05$); small letters compared groups in rows; Large letters compared groups in columns for various birds on a specific day; Italic number compared broiler male, broiler female and layers in columns on various days.

Discussion:

The LD50 values of salinomycin in broiler chickens and laying hens obtained in this study are similar to the values found by others (Bradley, 1992; Neuschl et al., 2001; Neuschl et al., 2002; Vaczi et al., 2006; Rajaian et al., 2009). The minor differences could be explained by differences in the age of the chickens used in each study and the method of analysis as four week old birds have been employed in other investigations and LD50 has been calculated using a double dose interpolation method according to Roth (1962). Potter et al. (1986) also reported a higher toxicity of salinomycin for younger turkeys compared to older ones.

Although there has been no report of an antidote or proven treatment regimen against ionophore toxicosis (Jones, 2001), the use of emetics (in small animal only) and activated charcoal or mineral oil in combination with saline cathartics, may decrease the absorption of ionophore drugs (Haward, 1993). Moreover, salinomycin induces toxicity by generating free radicals and disturbing the antioxidant defense, which could be effectively prevented by the use of zinc as an antioxidant (Kamashi et al., 2004).

The use of HD in the treatment of experimental salinomycin toxicosis in chickens was shown to be moderately efficient in the present study. This is reflected in the results depicted in Table 1 as the number of mortalities was decreased in groups receiving HD (Table 1). However, the difference in the mortalities were only significant ($P<0.05$) when all birds (broiler male and female and layers) were collectively analyzed statistically (Table 1).

Salinomycin, an ionophore coccidiostat widely used in chicken feed (Johansen et al., 2007), is a compound that acts by transporting alkali metal ions, resulting in an altered ionic gradient and a disturbed physiological process in coccidia (Pressman, 1976). Over dosage or accidental exposure of a non target species to the compound can lead to toxic syndromes (Novilla, 1992) that probably relate to the disturbance of the metabolism of ions within the tissues or to the oxidative damage (Kamashi et al., 2004).

One of the effects of ionophore is seen on energy metabolism. Alternation of the cellular ionic gradient by ionophores can deplete intracellular ATP levels (Bergen and Bates, 1984). As a result of cell membrane damage, an influx of sodium and calcium ions into cells may lead to cell death. Ionophore may also directly reduce mitochondrial oxidative phosphorylation in myocytes, resulting in a decrease in cellular respiration (Van Vleet and Frans, 1983). The primary target tissues are cardiac and skeletal muscles (Nicpon et al., 1997; Mendes et al., 2003).

Normal serum enzyme activity in birds is less than 230 IU/L for AST and less than 20 IU/L for ALT (Kaneko, 1997; Thrall, 2004), which is similar to the values found in this study in the control groups (Tables 2 and 3). Normal serum CK activity in birds is reported to be between 100 and 200 IU/L (Kaneko, 1997; Thrall, 2004), which is different from the values obtained in the control group in the present study. The high CK values in the control group may be due to the stress of bleeding and handling of birds. A lower decrease in AST and a higher decrease in CK at days 7 and 14 may be due to their half life and not because of the treatment. Basically, a decrease in the activities of the above enzymes is not valuable in clinical pathology (Thrall, 2004).

Intoxication with salinomycin caused an increase in the serum levels of AST, ALT and CK in broiler chickens and laying hens not treated with HD. In contrast, these effects are reversed in those groups receiving treatment with HD (Tables 2, 3 and 4).

Oral administration of various doses (1, 2 and 4 mg/kg) salinomycin in sheep has been shown to cause an increase in the level of serum AST, ALT and CK (Rajaian et al., 2009c). The highest value of these enzymes was obtained 616±40.8, 76.2±7.6 and 98.6±4.3, respectively. Increase in the levels of these enzymes

are probably due to hepatic and myocardial damages and the serum activity of CK may increase because of myopathy (Rajaian et al., 2009c). Rajaian et al. (2009b) also reported that salinomycin significantly increased the activities of ALT, AST and CK from 19.0±1.9, 301±16.6 and 409±34.7 IU/L to 74.7±9.4, 301±16.5 and 409±34.7 IU/L, respectively, 4 days following drug administration in female calves. In male calves receiving a larger dose (5 mg/kg) of salinomycin the enzyme activity of ALT, AST and CK was significantly increased from 21.3±0.5, 92.3±2.5, and 123.6±10.1 IU/L to 78.0±11.5, 316.0±24.6, and 385.0±38.4 IU/L respectively. The activities of ALT and CK were returned to normal values after 4 days, while AST activity remained high, even till the end of the experiment. Chickens receiving salinomycin with or without the administration of phenobarbital and chloraphenicol, showed no significant differences in the activities of AST, ALT and CK. (Rajaian et al., 2009a).

ALT is a cytoplasmic enzyme and AST is both a cytoplasmic and mitochondrial enzyme. The increase in the serum level of ALT and AST may indicate hepatic and/ or myocardial damage (Stockham and Scott, 2002). Elevated levels in AST and ALT in toxicosis with salinomycin in broilers might be due to oxidative damage by free radicals resulting in hepatocellular injury (Kmashi et al., 2004, Novilla, 1992, Lehel et al., 1995). The serum activity of CK was increased, probably due to the characteristic myopathy (Stockham and Scott, 2002; Valberg, 1996). A variety of insult (pathologic and iatrogenic) may damage muscle fibers and release CK from the muscle fiber (Stockham and Scott, 2002).

Values of serum AST and ALT in turkey affected by salinomycin are usually not elevated early in the clinical syndrome and should not be considered useful as an early indicator of muscle damage (Neufeld, 1992). However, Neufeld (1992) reported that the serum CK level is markedly elevated in clinically ill turkey (receiving 15.5 ppm salinomycin in their feed) and, therefore, may be a useful tool to confirm early muscle damage (Stokowsky, 2003).

Conclusion:

It is generally concluded that first, the administration of HD is partially effective in the treatment of salinomycin poisoning in chickens and second, serum AST, ALT and CK levels are increased due to salinomycin toxicosis, and treatment with HD counteracts these effects.

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