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Effects of Diacetoxyscirpenol and Fusaric Acid on Poults: Individual and Combined Effects of Dietary Diacetoxyscirpenol and Fusaric Acid on Turkey Poult Performance

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Abstract: Turkey poults were randomly placed in batteries and fed one of four dietary treatments: control (C); control plus 4ppm diacetoxyscirpenol (DAS); control plus 300ppm Fusaric Acid (FA); and control plus 4ppm DAS and 300ppm FA (FD). There were 10 poults per pen with 6 replicate pens per treatment. Individual BW, BW gains (BWG) and feed consumption by pen were determined at d6, d12, and d18. Period and cumulative feed to gain were calculated. Mouth lesions were scored for treatments at d18. On d18 poults were euthanized for determination of organ weights and jejunal histomorphometrics. FA had no effect on BW or BWG at any period compared to C. Poults fed FD had reduced BW and BWG compared to C, while poults fed DAS had lower BW than all treatments at every period. Poults fed FA or C had better feed to gain ($P<0.05$) than poults fed DAS or FD at d6. There were no differences among the treatments at d12 or d18. Poults fed FA had significantly lower relative intestine wt than poults fed the other diets, and significantly higher relative bursa wt at d18 when compared to poults fed DAS or FD. DAS, FA and FD altered intestinal architecture. Poults fed DAS or FD had higher mouth lesion scores than poults fed FA or C, but mouth lesion scores in DAS and FD poults were not different from each other. Dietary DAS resulted in decreased poult performance, while dietary FA had little or no effect. Fusaric acid fed in combination with DAS resulted in some protective effect towards DAS.

Key words: Diacetoxyscirpenol, fusaric acid, turkey, performance, intestinal histomorphometrics

Introduction

Molds, present in corn and other grains fed to poultry, produce mycotoxins that are detrimental to poultry production. After consumption of contaminated feed, the decreased weight and weight gain that results from poor health and performance are two characteristics with financial implications. One such genus of molds commonly found naturally occurring in feedstuffs is *Fusarium*, which produces a number of mycotoxins as secondary metabolites. Two mycotoxins produced by *Fusarium* species are diacetoxyscirpenol (Ueno *et al*., 1973) and fusaric acid (Hidaka *et al*., 1969).

4,15-diacetoxyscirpenol (DAS) is a type A tricothecene that has been characterized by its effects of reduced body weight gain and mouth lesions in chickens and turkeys when fed at a range of 1 to 4ppm DAS in the feed for up to 3 weeks (Ademoyero and Hamilton, 1991; Leeson *et al*., 1995; Kubena *et al*., 1997). DAS primarily inhibits protein synthesis at the ribosomal level, followed by a secondary disruption of DNA and RNA synthesis. It affects actively dividing cells of the oral cavity and gastrointestinal tract (Leeson *et al*., 1995). The time from exposure needed to provoke the development of mouth lesions through contact with contaminated feed has been reported to be a few days, with the number of mouth parts having lesions tripling within 2 wks(Ademoyero and Hamilton, 1991).

Fusaric (5-butylpicolinic) acid (FA) is considered to have low to moderate toxicity to poultry. The metabolite is a hypotensive agent due to its inhibition of dopamine-$-hydroxylase, a key enzyme in the regulation of the synthesis of the neurotransmitter norepinephrine, in adrenal glands (Hidaka *et al*., 1969). Chu *et al*. (1993) described a potentiation of the humoral immune response to ovine erythrocytes when FA was added to the feed at 35 ppm. Chicks' cell-mediated cutaneous response to phytohemagglutinin-P was reduced after FA was added to the feed at 35, 75, and 150 ppm. After injection into the lateral ventricle, FA produced a dose-dependent increase in feed intake (Bungo *et al*., 1999). However, FA given in the feed up to 400 ppm yielded no change in BW or body weight gains (BWG; Chu *et al*., 1993; Ogunbo *et al*., 1994).

Under field conditions, feed may be contaminated by more than one mycotoxin, whether this occurs through mixing individual ingredients each contaminated by one mycotoxin, or by having one feed ingredient contaminated with a mold capable of producing more than one mycotoxin (Ueno *et al*., 1973). Fusaric acid has been shown to be synthesized with other mycotoxins

Table 1: Composition of the treatment rations

Ingredient	Diet (%)			
	Control	Fusaric Acid	Diacetoxyscirpenol	Fusaric Acid + Diacetoxyscirpenol
Corn	45.2	45.2	45.2	45.2
Soymeal	39.8	39.8	39.8	39.8
Limestone	1.4	1.4	1.4	1.4
Poultry fat	2.0	2.0	2.0	2.0
Dical 18.5 Phos	2.2	2.2	2.2	2.2
Poultry meal	8.0	8.0	8.0	8.0
DL Methionine	0.2	0.2	0.2	0.2
Lysine	0.2	0.2	0.2	0.2
Salt	0.2	0.2	0.2	0.2
Choline Chloride	0.2	0.2	0.2	0.2
Minerals[1]	0.2	0.2	0.2	0.2
Vitamins[2]	0.2	0.2	0.2	0.2
Selenium[3]	0.2	0.2	0.2	0.2
Fusaric Acid[4]		0.03		0.03
Diacetoxyscirpenol[5]			0.004	0.004
	Calculated analysis			
Protein	27.91	27.91	27.91	27.91
ME (kcal/lb)	1,297.71	1,297.71	1,297.71	1,297.71
Fat	5.22	5.22	5.22	5.22
Methionine	0.68	0.68	0.68	0.68
Methionine + Cystine	1.13	1.13	1.13	1.13
Lysine	1.71	1.71	1.71	1.71
Calcium	1.44	1.44	1.44	1.44
Available Phosphorus	0.73	0.73	0.73	0.73
Sodium	0.13	0.13	0.13	0.13
Content by analysis				
Fusaric Acid[6] (mg/kg)		119		137
Diacetoxyscirpenol[7] (mg/kg)			5	5

[1]Minerals mix supplied the following per kilogram of diet: 120 mg Zn as $ZnSO_4$ H_2O; 120 mg Mn as $MnSO_4$ H_2O; 80 mg Fe as $FeSO_4$ H_2O; 10 mg Cu as $CuSO_4$; 2.5 mg I as $Cu(IO_3)_2$; 1.0 mg Co as $CoSO_4$. [2]Vitamin mix supplied the following per kilogram of diet when added at 0.2%: vitamin A, 6,600 IU; vitamin D_3, 2000 ICU; vitamin E, 33 IU; vitamin B_{12}, 19.8 mg; riboflavin, 6.6 mg; niacin, 55mg; d-pantothenate, 11mg menadione, 2mg; folic acid, 1.1mg; thiamine, 2mg; pyridoxine, 4mg; d-biotin, 126mg; ethoxyquin, 50mg. [3]Selenium premix supplied .21mg Se, as Na_2SeO_3. [4]added to fusaric acid and fusaric acid + diacetoxyscirpenol diets at a rate of 300mg/kg of finished feed. [5]Diacetoxyscirpenol added to diacetoxyscirpenol and fusaric acid+ diacetoxyscirpenol diets at a rate of 4mg/kg of finished feed. [6]Fusaric acid analyzed by gas chromatography for purity; average of 43% recovery rate based on calculated amendment. [7]Diacetoxyscirpenol analyzed by gas chromatography for purity; 100% recovery rate based on calculated amendment.

produced by *Fusarium* species (Porter *et al*., 1995). Fusaric acid has been shown to exhibit synergism with another *Fusarium* metabolite, fumonisin, after injection into fertile chicken eggs (Bacon *et al*., 1995). Synergism between FA and DAS on mortality has already been demonstrated in two species of insects that yielded a 4- to 7-fold increase in toxicity (Dowd, 1988). Since DAS and fusaric acid are common metabolites of the fungi, *Fusarium*, shown to be present in poultry feedstuffs, a study hypothesizing a possible synergistic toxicity between the two is warranted. The objectives of this study were to determine the individual and combined effects of diacetoxyscirpenol and fusaric acid on turkey poults d6 to d18.

Materials and Methods

Experimental design and diet preparation: This study was conducted under animal care and use guidelines established by North Carolina State University's Animal Care and Use Committee. The experiment was performed using 240, day-of-hatch Large White Hybrid turkey poults hatched from facilities located at North Carolina State University. The turkeys were individually weighed, wing-banded and randomly placed in electrically heated battery pens. Dietary treatments; control (C), DAS added at 4 ppm, FA added at 300 ppm, and a combination of 4 ppm DAS plus 300 ppm FA (FD), were assigned by Latin Square arrangement. These dietary concentrations of DAS, FA and FD were used

Table 2: Effect of dietary fusaric acid (FA), diacetoxyscirpenol (DAS) alone and in combination (FD) on BW (g) and BW gains (BWG, g) of poults

	BW		
Treatment	d6	d12	d18
Control	124.1[A]	247.8[A]	451.7[A]
Fusaric Acid	126.5[A]	255.3[A]	464.9[A]
Diacetoxyscirpenol	100.0[C]	193.1[C]	351.4[C]
FD	110.8[B]	215.3[B]	389.0[B]
Mean	115.7	228.9	416.1
SEM	1.2	2.2	3.8
	BWG		
Control	68.0[A]	123.2[A]	203.6[A]
Fusaric Acid	69.7[A]	129.0[A]	209.7[A]
Diacetoxyscirpenol	43.7[C]	92.2[C]	157.2[C]
FD	53.9[B]	103.6[B]	173.7[B]
Mean	59.3	112.5	186.8
SEM	1.2	1.2	2.0

[A, B, C]Means within a column with no common superscript differ significantly ($P < 0.01$)

Table 3: Effect of dietary fusaric acid (FA), diacetoxyscirpenol (DAS) alone and in combination (FD) on feed to gain ratios of poults

Treatment	d6	d12	d18
Control	1.04[B]	1.32	1.41[ab]
Fusaric Acid	1.05[B]	1.29	1.37[b]
Diacetoxyscirpenol	1.19[A]	1.25	1.49[a]
FD	1.15[A]	1.37	1.52[a]
Mean	1.10	1.31	1.45
SEM	0.02	0.03	0.02

[a,b]Means within a column with no common superscript differ significantly ($P < 0.05$). [A,B]Means within a column with no common superscript differ significantly ($P < 0.01$)

Table 4: Effect of dietary fusaric acid (FA), diacetoxyscirpenol (DAS) alone and in combination (FD) on relative intestine and bursa weights of poults

Treatment	Relative Intestine Wt	Relative Bursa Wt
Control	5.97[a]	0.22[ab]
Fusaric Acid	5.44[b]	0.23[a]
Diacetoxyscirpenol	6.13[a]	0.19[b]
FD	5.84[a]	0.20[b]
Mean	5.82	0.21
SEM	0.07	0.01

[a,b]Means within a column with no common superscript differ significantly.

because previous studies in this laboratory had demonstrated that they are levels that can be fed to poults without affecting mortality (Hagler, unpublished observations) .

There were 6 replicate pens of 10 turkey poults per dietary treatment, and the poults were grown to 18 d of age. The poults were fed a basal turkey starter diet (Table 1) that was found to be below detection limits for aflatoxin, fumonisin, deoxynivalenol, zearalenone, and T-2 toxin. The diet met or exceeded the National Research Council (1994) requirements for essential nutrients. The DAS was prepared from cultures of *Fusarium sambucinum* NRRL 13495 using the method of Richardson and Hamilton (1987), who confirmed the identity of the toxin by nuclear magnetic resonance and mass spectroscopy. The FA was purchased from Sigma-Aldrich (St. Louis, MO, USA). Toxin purity for the FA and DAS used in this experiment was determined by gas chromatography. The basal diet was combined with DAS and FA by dissolving each pure crystalline toxin in acetone, pipetting each over 0.45 kg of feed individually or in combination, thoroughly mixing, and letting the feed dry overnight in a shallow pan. After drying, these 0.45 kg quantities of feed were mixed with their respective dietary treatment assignments to produce the three treatments containing added toxins. Water was provided *ad libitum* via nipple drinkers in each pen.

Data collection and analysis: Individual BW, BW gains (BWG) and feed consumption by pen were determined at d6, d12, and d18. Period and cumulative feed to gain per pen were calculated through d12 and d18. Mortalities were recorded daily. Mouth lesions were scored for all treatments at d18 based on a five-point scale (0 = no lesions; 5 = severe lesions) by an individual with no knowledge of treatment assignments. At d18, after euthanasia by cervical dislocation and dissection, liver, spleen, bursa, intestinal, and jejunal weights were measured at d18.

After euthanasia, 10 poults per treatment were randomly selected across all treatments and pens and portions of their mid-jejuna prepared for histological analysis as described by Bird *et al*. (1994) in mice and modified for turkey poults by Fan *et al*. (1997). Jejunal segments were fixed in Carnoy's solution for 4 hours, sequentially dehydrated and and stored in 70% ethanol (vol/vol). Samples were then embedded with paraffin and cut into 5µm sections, mounted on a glass slide and then stained with Feulgen reagent and counter-stained with 0.05% Fast Green. A computerized microscropic image analyzer (Chemilmager™ 440, Alpha Innotech Corp., San Leandro, CA, USA) was used to determine villus planar perimeter length, villus width at mid-villus, villus height, height of enterocytes at mid-villus and supporting muscle layer thickness. Measurements on individual histomorphometric parameters were made from randomly selected slides exhibiting a mid-section plan of villi. Because of orientation of tissue samples, not all parameters could be measured from each section. No

Table 5: Histomorphometric analysis of jejunal tissue of poults fed fusaric acid (FA), diacetoxyscirpenol (DAS) alone or in combination (FD)‡

	Villus Planar Surface Area[1] (µ)	Villus Height[2] (µ)	Villus Width[3] (µ)	Serosal Thickness[4] (µ)	Crypt Depth[5] (µ)	Mid-Villus Enterocyte[6] Height (µ)
Control	1208±75.62	567±41.69	105±27.81	269±9.81[b]	57±3.17	101±9.66[a]
FA	1277±32.13	585±17.83	130±13.20	219±6.78[c]	56±3.30	41±3.07[b]
DAS	1271±72.87	575±43.38	123±32.12	328±6.99[a]	49±3.26	41±5.82[b]
FD	1161±96.395	509±61.35	45±42.05	241±8.10[bc]	46±4.29	MD*

‡ Means ± SEM [1]n=107; [2]n=102; [3]n=106; [4]n=209; [5]n=144; [6]n=109

[abc] treatments in columns with different superscripts differ (p <0.05) * MD = data not available

suitable sections for measuring mid-villus enterocyte height could be found for the FD treatment.

Statistical analysis of performance parameters, mouth lesions and relative organ weights were performed using the General Linear Models procedure of the SAS Institute, Inc. (1989). The statistical design was a factorial arrangement of treatments which included the main effects of treatment, level of battery and error. Relative organ weights were analyzed using covariate analysis with individual bird weight as the fixed variable. Means of performance parameters and relative organ weights were separated using the Least Squares Means procedure with significance accepted at $p<0.05$. Because of differences in sampling for histological analysis compared to all other parameters, the statistical analysis of histomorphometric data were conducted independently. Samples for histomorphometric analysis were collected from the jejuna of 5-7 birds per treatment and randomly selected across all pens. Slides for analysis of morphometric parameters were randomly selected based on appropriate spatial orientation of the fixed tissue samples. Replicate parameter measurements were made on each slide. Data were analyzed using a one-way analysis of variance (Statistix® version 8, 2003). Pairwise comparison of means was conducted using Tukey's Method with significance accepted at $p<0.05$.

Results

Effects on poult performance: There was no effect of FA on poult BW (Table 2) or BWG (Table 2) when fed at 300 ppm in the feed at d6, d12, or d18. However, there was a significant reduction in BW and BWG for poults fed the DAS diet for each period performance characteristics were measured ($P<0.01$). The combination diet, FA plus DAS (FD) yielded a significant recovery in BW and BWG at d6, d12, and d18 ($P<0.01$). At d6, the control diet and FA diet had a significantly better feed to gain ratio than the DAS and the FD diets (Table 3). At d18, poults fed the FA diet had a better feed to gain ratio than either the DAS or FD fed birds (Table 3), but no treatment diet was significantly different from control. There were no differences in cumulative feed to gain for d0-d12 or d0-d18 days.

Tissue and histomorphometric analysis: Fusaric acid significantly reduced relative intestinal weight compared to all other dietary treatments (Table 4). The FA treatment also increased relative bursa wt compared to the DAS and FD treatments, but no dietary treatment was different from control (Table 4). There were no significant differences in the relative wts of the liver, spleen, or jejunum (data not shown).

Histomorphometric analysis of jejunal tissue parameters were within the range of values noted in previous studies in this laboratory with d14 poults (Fan *et al*., 1997). Jejunal serosa in FA treated poults was 19% thinner (Table 5) than those of controls. DAS treatment resulted in 18-33% greater serosal thickness ($P\leq0.05$) compared to controls and FA treatments. There was a non-significant trend ($p = 0.07$) for decreased crypt depth for all treatments compared to controls (57µ vs 56µ, 49µ and 46µ for control, FA, DAS and FD, respectively). Both FA and DAS treatment decreased enterocyte height at mid-villus by 59% ($P = 0.05$; Table 5).

Mouth lesion scores: All treatments were scored for mouth lesions in order to show no cross contamination with DAS. All scoring was performed on a subjective scale of 0 for no visible lesions to 5 for the presence of severe lesions. Only treatments with DAS added were associated with mouth lesions. Since the poults fed the control and FA diets had no mouth lesions, the DAS and FD treatments were statistically compared to each other for mouth lesion scores. The two treatments were not significantly different from each other (DAS = 4.48; FD = 4.64).

Discussion

Fusarium species produce a vast array of mycotoxins, many of which are economically important in regards to animal production. If a mycotoxin is found in a contaminated feed source, there is a high chance of additional mycotoxins being present, produced by several or a single species of mold (Prelusky *et al*., 1994). Concentrations of individual mycotoxins are usually low enough not to cause problems with animal performance, but there is a potential for interactions

between metabolites that result in net effects of additive or even synergistic relationships. Fusaric acid is a common metabolite of several *Fusarium* species including *F. moniliforme*, *F. subglutinans*, and *F. oxysporum* and its simultaneous synthesis with other *Fusarium* toxins including fumonisins and trichothecenes has been reported (Porter *et al*., 1995).

After the addition of FA to the feed at 300 ppm in the current study, there was no significant effect on BW or BWG. These results concur with those reported by Chu *et al*. (1993), who reported no effect of on BW and BWG when chicks were fed up to 150 ppm, and Ogunbo *et al*. (1994) who reported similar results with chicks and poults fed up to 400 ppm.

The addition of DAS to the turkey starter diet had expected negative results of reduced weight gain and severe mouth lesions. Similar results were reported by Kubena *et al*. (1997). After feeding 4 ppm DAS, a significant reduction in BWG was seen at 1 wk and cumulative reductions of 23% in BWG seen through d20. Only treatments with DAS were associated with mouth lesions, in contrast to the lack of oral lesions with FA. The two DAS treatments were not significantly different from each other (DAS = 4.48; FD = 4.64). Kubena *et al*. (1997) reported oral lesion scores for the DAS treatment were 3.19 on a 1 to 4 scale. Sklan *et al*. (2003) reported modest increases in growth, but not feed efficiency, in poults fed diets with 0.423 ppb to 0.860 ppb. In addition they observed significant oral lesions after 7 days.

In the present study, the effects seen after the addition of both FA and DAS to the diet were unexpected. The FD treatment resulted in significant recovery in BW and BWG at each day measured, which included feeding at levels less than the maximum used in previous publications. However, the combination diet impaired feed to gain at d6 compared to the control diet.

Histomorphometric parameters indicate that DAS, FA and FD diets alter physiological function in the intestinal tract (Table 5). Hoerr *et al*. (1981) reported that acute administration of large dosages of DAS (2.7 mg/kg body weight) to d7 broilers, via gavage, resulted in villus atrophy and decreased epithelial mitosis within 24 hours. In the present study, the serosal layer was decreased with FA whilst it increased with DAS. The trend ($P = 0.07$) for decreased crypt depth along with substantial decreases in ($P<0.05$) enterocyte height at mid-villus indicate that both DAS and FA are affecting the propagation and development of enterocytes. Enterocyte height at mid-villus is positively correlated with cell maturation (Bird *et al*., 1994). The 59% decrease in enteroctye height associated with both FA and DAS is highly indicative that these mycotoxins are altering digestive and absorptive function (Table 5). This is supported by the work of Sklan *et al*. (2003) who reported increased proliferating cells in jejunal crypts of d32-d34 poults fed DAS at 0.860 ppm. Increased production of enterocytes in the crypts of villi could result in faster migration of cells up the villus stalk at rate that precludes normal development. Sklan *et al*. (2003), however, reported that jejunal enterocyte migration rate was not affected in DAS poults. Although Sklan *et al*. (2003) administered DAS at concentrations that were only 20% that used in this study, their observations indicate the decrease in enteroctye height at mid-villus (Table 5), had more to do with alterations in cell metabolism rather than migration rate. Tricothecene mycotoxins are known to decrease protein synthesis, inhibit DNA and lipid synthesis and inactivate some enzymes (Ueno, 1977), which could affect enterocyte size and maturation.

Bacon *et al*. (1995) demonstrated a synergistic toxic interaction between and fusaric acid fumonisin B_1 in the fertile chicken egg. Injected alone, fusaric acid resulted in 2% mortality. While keeping the fusaric acid dose constant, a dose dependent mortality curve was observed as fumonisin B_1 was combined at increasing levels. Synergism was also demonstrated between fusaric acid and DAS in insects (Dowd, 1988). Feeding both fusaric acid plus DAS caused an increase in mortality from 5% with DAS alone to over 20% with fusaric acid plus DAS combined.

The study of interactions between mycotoxins often leads to a better understanding of how mycotoxicoses would present themselves in production situations, where conditions are favorable for the mixing of fungal metabolites. It is difficult to predict the response from combined toxins based on their individual responses. The combination of mycotoxins used in this study did not produce an expected increased toxicity, which could have been described as addition, potentiation or synergism (Klaassen and Eaton, 1991). Nor did the study demonstrate the ability of one toxin (DAS) to mask any effects of another, such as fusaric acid. It is hypothesized that fusaric acid antagonized the toxic actions of DAS with regards to BW and BWG. Even though the poults had the same visual score for mouth lesions, they were able to significantly increase their feed intake and wt gain throughout the length of the study compared to birds on the DAS diet.

We interpret the current data as demonstrating that for poult performance parameters, fusaric acid plus diacetoxyscirpenol may be less toxic than the individual toxins. For many tissues, neither DAS or FA, alone or in combination, had any effect on relative organ weights. However, diacetoxyscirpenol produced the same severity of mouth lesions whether alone or with FA in the diet of turkey poults. Further work is needed to fully evaluate the mycotoxin interaction relationships of FA with other *Fusarium* metabolites and their effects on poult performance.

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Abbreviation Key: DAS = diacetoxyscirpenol; FA = fusaric acid; FD = fusaric acid plus diacetoxyscirpenol