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Original Research

Accumulation and Degradation of Thiabendazole Residues in Eggs in Administered Layer Hens

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Abstract

Administration of thiabendazole (TBZ) to laying hens may cause accumulation of the drug residues in eggs. Twenty five week old hens (n=6) were administered with a single oral dose of 75 mg TBZ/day/layer hen for 5 consecutive days and its residues in eggs were quantified by HPLC-FD. The highest TBZ (0.4308±0.0253 ppm), below maximum residue limit (0.0886±0.0161 ppm) and below limit of detection (LOD) residue concentrations in eggs were observed on mean time of 127.54, 177.62 and 252.58 h after first feeding, respectively. The highest TBZ concentration (0.5260 ppm) and total residue on any day from 2 to 9 day in the entire egg white portion were significantly (P<0.01) higher than those in the yolk. The highest residue concentrations as well as the highest total residue in egg albumin (0.5944 ppm), yolk (0.6587 ppm) and whole egg (0.5867 ppm) were quantified. The highest TBZ concentration (0.5260 ppm) as well as total TBZ residue on any day from day 2 to day 9 in the entire white portion of egg were significantly (P<0.01) higher than those in the yolk . Egg white, yolk and whole egg from the TBZ fed hens had residues at 50.71 to 153.50, 75.62 to 153.50 and 50.71 to 153.50 h after first feeding, respectively. The highest concentration TBZ residue in whole egg is 0.4308±0.0253 ppm and cumulative residue is 8.1886±6.5385 ppm and also calculated in microgram is useful to show as per the standard values. The work indicated that safe dose and days to consume egg. Safe time/days can be reduced for consuming eggs after administration of thiabendazole by using different types of decontamination techniques.

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INTRODUCTION

Use of several veterinary drugs on food-producing animals, grown intensively by modern animal husbandry practices, is common to many countries (Mellon *et al.,* 2001; Solomon *et al.,* 2002; Wachtel *et al.,* 2002; Goldman 2004 and Cam *et al.,* 2009). Thiabendazole (TBZ), registered in many countries, is used as a broad-spectrum anthelminthic agent to control parasitic infestations in animals. It is also used as antifungal as well as growth promoting agent on animals. Inappropriate use of veterinary drugs on animals as well as in feeds and foodstuffs has led to their increased residues in human food commodities like eggs in many countries including India (Schaellibaum 1990; Lidong 1992; Paige 1994; Reja-Sanche *et al.,* 1995 and Okerman *et al.,* 2001).

As a direct hazard, chronic and acute toxicities such as teratogenesis, carcinogenicity, liver hypertrophy, thyroid hyperplasia, immuno-suppression and decreased foetal as well as maternal body weight have been associated with varying exposures to benzimidazoles including TBZ as a major compound. The most concern for indirect hazard from the use of antibiotics in animal husbandry is the development of drug-resistant pathogens in food animals (Kulshrestha 1990; Brady *et al.,* 1993; Bordas *et al.,* 1997; Gogus *et al.,* 2000 and Wrigley *et al.,* 2006), which in turn, may lead to antibiotic-resistant pathogen in animal-derived foodstuffs and human beings (Willis *et al.,* 1999; Rajashekara *et al.,* 2000; Swartz, 2002; Schlegelova, 2002 and Horby *et al.,* 2003).

Distribution of veterinary drug residues and their dissipation from various parts of animal's body, depending upon type of drugs, animal, organ, meat portion, milk, egg etc., may give rise to their detectable residue levels (Takahashi *et al*., 1991; Donoghue *et al.,* 1999; Kuehn *et al*., 2000; Cornelis *et al.,* 2000 and Roudaut *et al.,* 2000). Glomerullar filtration and tubular secretion are the major routes of administration of TBZ, faecal elimination through enterohepatic recycling and bone sequestration are the secondary routes for the elimination of administered TBZ from animal body (Bai *et al.,* 2010). Conversely, oral administration of TBZ to sheep, cattle, goats, dogs and humans results rapid absorption from the GI tract, and almost all the entire quantity is recovered from urine and faeces. The hydroxylation of the benzimidazole ring at the 5-position to form 5-OH TBZ and subsequent conjugation to form the glucuronide and sulfate are the major metabolic steps. In a study an oral administration of 3.19

mg of [^{14}C] TBZ daily to laying hens for 10 consecutive days showed an average recovery of 96.6% of the total administered dose, and about 99.6% of this recovered dose was found in the excreta, in the form of both unconjugated (3.4 mg/kg) and conjugated (4.4 mg/kg) 5-OH TBZ (Halls *et al.,* 1991a; Chukwudebe *et al.,* 1994 and Bai *et al.,* 2010). Cumulatively, the total residues found in the tissues and eggs accounted for about 0.4% or less of the ^{14}C. The total residues in eggs attained a level of about 0.1 mg/kg by day 2 and remained relatively unchanged throughout the next 8 days. The residues in tissues and eggs consisted mainly of unconjugated 5-OH TBZ, unmetabolized TBZ and benzimidazole at maximum concentrations, in the kidneys, of 0.4, 0.11 and 0.12 mg/kg respectively. In an animal transfer study, chickens (males and females) treated continuously for 7 weeks with TBZ at levels corresponding to 2, 20, 200 and 2000 ppm in the feed (Yang *et al.,* 2011), showed the sum of TBZ and 5-OH TBZ including its conjugate as 20-28 ppb in fat taken from different body parts, 17-23 ppb in a 1:1 mixture of breast and leg meat, and 60-80 ppb in liver at the 20 mg/kg feed level. Neither TBZ nor its related residues are likely to persist in milk, eggs or edible tissues because of their relatively low concentrations and rapid elimination. Present study was undertaken to find out the accumulation and degradation levels of TBZ in layer chicken (BV 300) administered with a dose of 75 mg per bird per day for 5 consecutive days.

MATERIALS AND METHODS

HPLC grade water filtered through 0.2 µm (Qualigens Fine Chemicals, Glaxo-SmithKline Pharmaceuticals Ltd), HPLC grade acetonitrile and methanol (Ranbaxy Fine Chemicals Ltd, SAS Nagar, India), filtered through a 0.2 µm membrane) purchased from Sigma-Aldrich Corporation) were used. Mobile phase was prepared and filtered through 0.22 µm Millipore Durapore solvent filters (disc, 47 mm, 9.6 cm^2 filtration areas) under vacuum with Millipore All-glass Filter unit, degassed. Analytical standard thiabendazole (Sigma-Aldrich) was dissolved in HPLC grade methanol to get 1000 ppm neat stock standard corrected to 100% purity and stored at -18^{o}C in epandorff vials for a maximum period of 1 week. Each time working standard solutions were prepared a fresh from the stock standard.

Layer Chicken: Eight (6 experimental and 2 control) numbers of 25 week old birds of strain BV 300 were randomly selected from a flock of 9740 birds from a commercial local poultry farm for TBZ feeding trial. The birds were fed with a diet as in Table 1.

Table 1: Diet composition

Feed Ingredients	Quantity, % w/w
Broken maize	50
Deoiled sunflower cake	15
Deoiled soya cake	15
Broken rice	9
Shell grits	7.9
Mineral mixture	2.5
Common salt, iodised at 30 ppm	0.4
Vitamin premixes (A, D, E, K, B complex and probiotics)	0.05
Liver stimulant (hepatocare)	0.05
Toxin binder (UTPP)	0.05
Lysine and methionine (Biometh)	0.05

TBZ Administration: Thiabendazole (MW 201.25, >99% purity) was procured from Sigma-Aldrich Inc, St. Louis, USA. TBZ solution/suspension of 25000 ppm was prepared in distilled water, 3 ml of which was used to administer each of 6 experimental birds with a single oral dose of 75 mg TBZ per bird per day for 5 consecutive days.

Design of Experiment and Statistical Analysis: Each of 6 experimental and 2 control birds were individually housed in a medium mesh (2 cm square) GI cage of 22"x20"x20" (LxWxH), and cages were randomly placed in a properly lit and ventilated animal experiment room. Birds were administered with TBZ at 11 o' clock daily for 5 consecutive days. Live bird weight at the time of feeding, egg weight and laying time were recorded. Wherever egg laying time was not noticed actually, especially if at night, it was calculated by extrapolation from the previously or subsequently noted actual laying times. Eggs were collected from the first day to the day of non-detectable residue level, weighed and immediately stored at 5-6°C. Each day's eggs were broken, separated into the albumin and the yolk, which were weighed and used for analysis of TBZ residue. Once the residue level reached the non-detectable levels in egg, the birds were slaughtered and residue levels in breast meat, leg meat and liver were analyzed for TBZ residue by HPLC- fluorescence detector (Arenas *et al*., 1995).

Bird Sacrifice: Bird was sacrificed once the TBZ residue in the eggs reached below detection limit no need for monitoring the day now.

RESULTS AND DISCUSSION

Accumulation of TBZ in albumin and yolk of eggs obtained from administered layer hens from after first day of TBZ feeding to till non-detectable days (11th day) and from scarified hens at the end of experiment were presented in the form of both individual concentration as well as total residue levels. Subsequently quantified the TBZ levels in eggs on different times (hours) after the administration were shown table 2.

TBZ residue concentration (ppm) as well as total TBZ residue in entire portion of white, yolk or whole egg (white + yolk) with respect to the mean time after first TBZ administration were shown in table 2. TBZ residue was not detected in egg white and yolk on day 1 and day 11 after a mean time of 1.96 and 252.58 h from first feeding, respectively, and non-detectable residue levels were considered as nil residues for statistical analysis and interpretation. In case of egg white, TBZ residues concentration of 0.0888 ppm (i.e., 2.6203 µg total residue in the entire white portion) appeared on day 2 (after mean time of 25.87 h from first feeding), reached a maximum concentration level of 0.5260 ppm (i.e., 15.5925 µg total residue) on day 6 (after 127.54 h from first feeding) and declined thereafter to 0.0108 ppm concentration level (i.e., 0.2996 ug total residue) on day 10 (after 227.62 h from first feeding) before reaching non-detectable level on day 11. Similarly for egg yolk, TBZ residues concentration of 0.0215 ppm (i.e., 0.2964 ug total residue in the entire yolk portion) appeared on day 2 (after mean time of 25.87 h from first feeding), reached a maximum concentration level of 0.2157 ppm (i.e., 2.8544 µg total residue) on day 6 (after 127.54 h from first feeding) and declined thereafter to 0.0144 ppm concentration level (i.e., 0.1899 µg total residue) on day 10 (after 227.62 h from first

Table 2: TBZ residue in eggs and their components (n=6)

Day and Time of Laying from First Feeding	TBZ Concentration (TC), ppm			TBZ Concentration Ratio (TCR) White/ Yolk (TCW/TCY)
	Egg White (TCW)	Egg Yolk (TCY)	Whole Egg (TCT)	
Day 1, 1.96±1.17 h	0.0±0.0^{A}	0.0±0.0^{A}	0.0±0.0^{A}	-
Day 2, 25.87±0.66 h	0.0888±0.0176^{FG}	0.0215±0.0064^{CD}	0.0675±0.0101^{EF}	4.6323±2.1717^{de}
Day 3, 50.71±1.16 h	0.3197±0.0380^{LM}	0.0541±0.0139^{E}	0.2314±0.0254^{K}	6.2644±1.9614^{e}
Day 4, 75.62±0.93 h	0.3859±0.0438^{MN}	0.1194±0.0188^{GH}	0.3025±0.0318^{L}	3.2871±0.5345^{d}
Day 5, 101.67±1.02 h	0.4801±0.0370^{OP}	0.1906±0.0231^{IJK}	0.3944±0.0310^{N}	2.5405±0.2608^{d}
Day 6,127.54±1.62 h	0.5260±0.0360^{P}	0.2157±0.0290^{JK}	0.4308±0.0253^{NO}	2.4871±0.4799^{d}
Day 7, 153.50±2.35 h	0.1853±0.0288^{IJK}	0.1439±0.0310^{HI}	0.1724±0.0261^{IJ}	1.3171±0.2429^{c}
Day 8, 177.62±3.35 h	0.0965±0.0168^{G}	0.0697±0.0164^{EFG}	0.0886±0.0161^{FG}	1.4117±0.2142^{c}
Day 9, 201.37±4.89 h,	0.0157±0.0051^{BC}	0.0520±0.0105^{E}	0.0267±0.0046^{D}	0.3123±0.1199^{a}
Day 10, 227.62±3.90 h	0.0108±0.0024^{B}	0.0144±0.0029^{BC}	0.0120±0.0024^{B}	0.7559±0.1021^{b}
Day 11, 252.58±4.58 h	0.0±0.0^{A}	0.0±0.0^{A}	0.0±0.0^{A}	-
Grand Mean, day 2 to 10, N=6X9	**0.2343±0.1910^{II}**	**0.0979±0.0717^{I}**	**0.1918±0.1511^{II}**	**2.5565±2.0591**

Mean±SD (n=6) values of TBZ concentrations (TC), carrying different superscripts A, B, C, ….. vary significantly (*P*<0.01) or 1, 2, 3,…. vary significantly (*P*<0.05). Mean±SD (n=6) values of TBZ concentration ratio (TCR = TCW/TCY) in a particular column, carrying different superscripts a, b, c, ….. vary significantly (*P*<0.01). Grand mean±SD (N=6X9) values of TBZ concentrations in a particular row , carrying different superscripts I, II, III, ….. vary significantly (*P*<0.05).

feeding) before reaching non-detectable level on day 11. It showed that TBZ residue in the egg white appeared faster and at a significantly (*P*<0.01) higher concentration level than that in the yolk table 3 (Himanish Das *et al.,* 2008).

Furthermore, TBZ residue dissipated faster from the white than from the yolk due to degradation/dissipation of thiabendazole. The highest TBZ concentration (0.5260 ppm) as well as total TBZ residue on any day from day 2 to day 9 in the entire white portion were significantly (*P*<0.01) higher than those in the yolk (table 2 and 3). The egg white, the yolk and the whole egg contained the TBZ residue greater than the USEPA maximum residue limit (MRL) of 0.100 ppm in egg for TBZ (including 5-OH TBZ) on day 3 to day 7 (50.71 to 153.50 h), on day 4 to day 7 (50.71 to 153.50 h) and day 3 to day 7 (50.71 to 153.50 h) after first feeding, respectively Rey-Grobellet *et al.,* (1996). In other words, the egg white, the yolk and the whole egg from the hens, fed with a dose of 75 mg TBZ per day per bird for 5 days, had violative residues on day 3 to day 7 (50.71 to 153.50 h), on day 4 to day 7 (50.71 to 153.50 h) and day 3 to day 7 (50.71 to 153.50 h) after first feeding, respectively table 2. Mean weights of whole egg, egg without shell, white and yolk with respect to mean time after first TBZ administration. No significant effect due to the drug administration on birds' live weight, laying time and egg weights during the entire experiment was observed.

Table 3: TBZ residue in eggs and their components

Day and Time of Laying from First Feeding	TBZ Residue Concentration, ppm			TBZ Total Residue, µg		
	Egg White (WC)	Egg Yolk (YC)	Whole Egg without Shell (TC)	Egg White (WQ)	Egg Yolk (YQ)	Whole Egg without Shell (TQ)
Day 1, 1.96±1.17 h	0.0±0.0^{A}	0.0±0.0^{A}	0.0±0.0^{A}	0.0±0.0^{a}	0.0±0.0^{a}	0.0±0.0^{a}
Day 2, 25.87±0.66 h	0.0888±0.0176^{FG}	0.0215±0.0064^{CD}	0.0675±0.0101^{EF}	2.6203±0.5041^{ij}	0.2964±0.0917^{bc}	2.9166±0.4196^{ij}
Day 3, 50.71±1.16 h	0.3197±0.0380^{LM}	0.0541±0.0139^{E}	0.2314±0.0254^{K}	9.3450±1.3531^{lm}	0.7345±0.2203^{def}	10.0795±1.4755^{mn}
Day 4, 75.62±0.93 h	0.3859±0.0438^{MN}	0.1194±0.0188^{GH}	0.3025±0.0318^{L}	10.946±1.1419^{mn}	1.5548±0.3131^{gh}	12.5008±1.3335^{no}
Day 5, 101.67±1.02 h	0.4801±0.0370^{OP}	0.1906±0.0231^{IJK}	0.3944±0.0310^{N}	14.7666±1.3693^{op}	2.5403±0.4616^{ij}	17.3070±1.6610^{pq}
Day 6, 127.54±1.62 h	0.5260±0.0360^{P}	0.2157±0.0290^{JK}	0.4308±0.0253^{NO}	15.5925±0.8510^{p}	2.8544±0.4573^{j}	18.4470±0.9598^{q}
Day 7, 153.50±2.35 h	0.1853±0.0288^{IJK}	0.1439±0.0310^{HI}	0.1724±0.0261^{IJ}	5.3241±0.9303^{k}	1.8807±0.4484^{h}	7.2048±1.2045^{kl}
Day 8, 177.62±3.35 h	0.0965±0.0168^{G}	0.0697±0.0164^{EFG}	0.0886±0.0161^{FG}	2.7911±0.6085^{ij}	0.8473±0.2246^{ef}	3.6387±0.8009^{j}
Day 9, 201.37±4.89 h	0.0157±0.0051^{BC}	0.0520±0.0105^{E}	0.0267±0.0046^{D}	0.4615±0.1710^{cd}	0.6521±0.1085^{de}	1.1136±0.2005^{fg}
Day 10, 227.62±3.90 h	0.0108±0.0024^{B}	0.0144±0.0029^{BC}	0.0120±0.0024^{B}	0.2996±0.0812^{bc}	0.1899±0.0517^{b}	0.4894±0.1267^{cd}
Day 11, 252.58±4.58 h	0.0±0.0^{A}	0.0±0.0^{A}	0.0±0.0^{A}	0.0±0.0^{a}	0.0±0.0^{a}	0.0±0.0^{a}

Mean±SD (n=6) values of TBZ total (TT), carrying different superscripts A, B, C, ….. vary significantly (*P*<0.01). Mean±SD (n=6) values of TBZ total ratio (TTR = TCW/TCY) in a particular column, carrying different superscripts a, b, c, ….. vary significantly (*P*<0.05). Cumulative residue (from hens on from day 2 to day 11), mean±SD (N=6X9) values of TBZ total residue in a particular row, carrying different superscripts I, II, III, ….. vary significantly (*P*<0.01).

Table 4: TBZ residue in eggs and their components

	TBZ Residue t		
	White	**Yolk**	**Whole Egg**
Highest residue concentration (ppm), n=6	0.5260 ± 0.0360^{c3}	0.2157 ± 0.0290^{a1}	0.7308 ± 0.0253^{b2}
Highest total residue (µg), n=6	15.5925 ± 0.8510^{c}	2.8544 ± 0.4573^{a}	18.4470 ± 0.9598^{d}
Cumulative residue Mean±SD (µg), n= 60	6.9052 ± 5.7154^{B}	1.2834 ± 0.9659^{A}	8.1886 ± 6.5385^{B}
Cumulative residue of 54 eggs (TBZ) (ug)	372.88	69.30	442.18
Cumulative residue of 54 eggs (TBZ) (as % of drug fed)	0.0994%	0.0185%	0.1179%

1% a, b, c, ….; 5% 1, 2, 3,…. and 1% A, B, C….TBZ

CONCLUSIONS

No significant effect due to TBZ administration was observed on birds' live weight, laying time and egg weight during the experiment. Upon TBZ administration, the highest residue (0.4308±0.0253 ppm), the < MRL (0.1 ppm) residue (0.0886±0.0161 ppm) as well as the < LOD residue concentrations in eggs were observed in the mean time of 127.54, 177.62 and 252.58 h after first feeding, respectively. The highest TBZ concentration (0.5260 ppm) as well as total TBZ residue on any day from day 2 to day 9 in the entire white portion were significantly (P<0.01) higher than those in the yolk (table 2 and 3). Egg white, yolk and whole egg from the TBZ treated hens had violation residues on 50.71 to 153.50, 75.62 to 153.50 and 50.71 to 153.50 h after first feeding, respectively. The highest concentration of TBZ residue in whole egg was observed 0.4308±0.0253ppm and the cumulative residue 8.1886±6.5385ppm, and also calculated in microgram is useful to show as per the standard values (table 4).

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