«Research Note»

The Biological Half-Life of Residual Drug in Eggs; Proposal of an Equation Predictable for the Half-Lives of Various Drugs

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The relationship between the biological half-lives of various drugs in a whole egg and the drug contents in egg yolk and albumen, which have been presented in many papers, was examined.

The regression analysis indicated a highly significant relationship ($P < 0.01$) between the observed half-lives and the ratio of drug contents between egg yolk and albumen ($C_{y/a}$), and proposed was the following equation of the half-life (days) = $1.50 \cdot C_{y/a}^{0.25}$. Where, $C_{y/a}$ is the drug content ratio in egg yolk to in albumen at the withdrawal.

The half-lives of drugs in a whole egg can be easily predicted as far as their contents in the yolk and albumen of the egg laid at the withdrawal initiation of drugs is known.

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Key words : biological half-life, drug residue, egg yolk, albumen, whole egg

Introduction

In recent years, the use of various drugs in poultry farming has increased to prevent diseases of poultry. As a result, there is concern that residues of these drugs may be retained in eggs derived from treated poultry. To produce eggs free from drug residues, it is necessary to determine the biological half-life in a whole egg, which is now to be the most reliable pharmacokinetic parameter for the withdrawal time of drug after administration.

In our previous papers (FURUSAWA *et al.*, 1994 ; FURUSAWA and MUKAI, 1995 b), it was presented that biological half-lives of both sulphamonomethoxine (SMM) (the half-life = 0.9 days) and sulphadimethoxine (SDM) (1.0 days) in a whole egg were much shorter than those of other drugs, such as decoquinate (DEC) (3.8 days) and nicarbazine (NCZ) (4.2 days) (YOSHIDA, 1988).

Remarkably higher contents of the former 2 drugs (SMM and SDM) in albumen than in egg yolk (FURUSAWA *et al.*, 1994 ; FURUSAWA and MUKAI, 1995 a, b), and lower contents of the latter 2 drugs (DEC and NCZ) (NOSE *et al.*, 1982 ; YOSHIDA, 1988) in

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albumen than in egg yolk were also noticed. The high content in egg yolk than in albumen seemed to lead to prolong the half-life in a whole egg, and vice versa. The findings strongly suggest that the half-life in whole egg tends to be influenced by the ratio of drug contents in egg yolk and in albumen. We hypothesized that this ratio may be an important parameter for determining biological half-lives values of the drugs in a whole egg.

The purpose of this work was to evaluate the application of this ratio to various drugs, based on the data generated in our laboratory as well as other researchers.

Materials and Methods

Drugs and their depletion data

The data on the depletion of 13 drugs (4 antibiotics and 9 synthetic antibacterials) in whole egg and their contents (mg/kg : ppm) in egg yolk and albumen, which had been reported by us and other researchers, were utilized in this study (Table 1).

Data analysis

As biological half-lives in a whole egg for pyrimethamine (PYR) (NAGATA *et al.*, 1992) and sulphamethoxazole (SMX) (OIKAWA *et al.*, 1977) have not been reported, these values were calculated by using the depletion data shown in the respective papers according to the method described in our previous paper (FURUSAWA *et al.*, 1994).

A linear regression analysis was carried out between natural logarithm ($\ln$) of the ratio of drug content in egg yolk to albumen at the withdrawal ($C_{y/a}$) and $\ln$ of the observed biological half-life ($t_{1/2}$) of the drug in a whole egg.

The computer programs used in analysis are described by FURUSAWA *et al.* (1994).

Results

A significant linear relationship ($P < 0.01$) between $\ln C_{y/a}$ and $\ln$ of the observed biological half-life ($t_{1/2}$, days) of the drug in whole egg (Table 1) was observed. This relationship could be described by Equation 1, which was then transformed into Equation 2.

$$\ln (\text{the half-life}) = 0.41 + 0.25 \cdot \ln C_{y/a} \quad (r = 0.95^{**}) \quad \text{.....[1]}$$

$$\text{The half-life (days)} = 1.50 \cdot C_{y/a}^{0.25} \quad \text{.....[2]}$$

Using Equation 1, the biological half life in whole eggs for 13 drugs was predicted by individual $C_{y/a}$. Table 2 represents the predicted values termed as $T_{1/2}$ with their 95% confidence intervals, as well as the observed biological half-life ($t_{1/2}$).

No statistically significant difference between the predicted values ($T_{1/2}$) and those of the observed ($t_{1/2}$) was demonstrated ($P > 0.05$, Table 2). Therefore, Equation 2 was shown to be very useful to determine the half-lives of 13 drugs in whole egg.

Discussion

To obtain eggs free from drug residues, an appropriate withdrawal time for the drugs must be established. Traditionally, biological half-lives of various drugs used in poultry have been determined by drawing the depletion profiles in eggs by measuring the drug contents at various days after the withdrawal. Simpler and more accurate

Table 1. The experimental design of 13 drugs administrated orally to laying hens, the drug contents in egg yolk and albumen at the withdrawal, and the biological half-lives in whole egg

Drug	Administration			Drug contents ^a				
	Route	Dosage	Duration (days)	Egg yolk	Albumen	C_y/a^b	$t_{1/2}^c$	
Antibiotics :								
Chlortetracycline (CTC)	Feed	8,000 mg/kg diet	7	0.27	0.23	1.2	1.6	(1) ^d
Oxytetracycline (OTC)	Feed	4,000 mg/kg diet	7	1.08	0.81	1.3	1.1	(2)
Spiramycin (SP)	Water	400 mg/l water	5	1.41	0.67	2.1	2.4	(3, 4)
Tylosin (TS)	Feed	8,000 mg/kg diet	7	5.20	5.20	1.0	1.3	(5)
Synthetic antibacterials :								
Amprolium (AMP)	Feed	100 mg/kg diet	14	0.59	0.05	13.1	2.8	(6)
Decoquinat (DEC)	Feed	40 mg/kg diet	14	0.61	0.02	33.9	3.8	(6, 7)
Dinitolmide (DTM)	Feed	125 mg/kg diet	14	1.57	0.15	10.5	3.1	(6, 7)
Nicarbazine (NCZ)	Feed	200 mg/kg diet	14	25.80	0.43	60.0	4.2	(6, 7)
Pyrimethamine (PYR)	Feed	1 mg/kg diet	14	0.23	0.02	11.7	2.5 ^e	(8)
Sulphadimidine (SDD)	Bolus ^f	100 mg/kg BW	5	4.20	33.60	0.1	1.1	(9)
Sulphamethoxazole (SMX)	Feed	2,000 mg/kg diet	5	1.80	19.90	0.1	0.9 ^e	(10)
		4,000 mg/kg diet	5	2.90	39.00	0.1	0.9 ^e	(10)
Sulphamonomethoxine (SMM)	Feed	400 mg/kg diet	5	1.49	6.87	0.2	0.9	(11)
Sulphadimethoxine (SDM)	Feed	400 mg/kg diet	5	1.70	4.62	0.3	1.0	(12)

^a Average drug content (ppm : mg/kg) of egg laid at the withdrawal.

^b The drug content ratio in egg yolk to in albumen.

^c The observed biological half-life (days) in whole egg which have been presented in elsewhere.

^d References : 1, YOSHIDA *et al.*, 1973c ; 2, YOSHIDA *et al.*, 1973b ; 3, ROUDAUT and MORETAIN, 1990 ; 4, YOSHIDA *et al.*, 1971 ; 5, YOSHIDA *et al.*, 1973a ; 6, NOSE *et al.*, 1982 ; 7, YOSHIDA, 1988 ; 8, NAGATA *et al.*, 1992 ; 9, GEERTSMA *et al.*, 1987 ; 10, OIKAWA *et al.*, 1977 ; 11, FURUSAWA and MUKAI, 1995b ; 12, FURUSAWA *et al.*, 1994.

^e The values for PYR (NAGATA *et al.*, 1992) and SMX (OIKAWA *et al.*, 1977) were calculated by using the depletion data shown in the respective papers according to the method described in previous paper (FURUSAWA *et al.*, 1994).

^f Administered in capsules as a single dosage daily.

methods are needed to replace these time consuming depletion trials. In the present study, we tried to introduce a "general equation (the biological half-life in whole egg)" which may be calculated only from the data of the drug contents in egg yolk and albumen at the day of drug withdrawal.

A typical depletion profile for SMM (FURUSAWA and MUKAI, 1995b) in egg yolk, albumen and the whole egg is presented in Figure 1. Depletion profile of SMM in egg yolk differs from that in albumen. Drug contents in egg yolk decreased almost linearly with relatively slow depletion after the withdrawal, while those in albumen decreased exponentially with rapid depletion. Generally, a slow depletion pattern in egg yolk and a rapid depletion in albumen is observed. This concept (kinetic behavior) may come from the difference of the process forming the two components of eggs. In the case of

Table 2. Comparison of the observed ($t_{1/2}^b$) and predicted ($T_{1/2}^c$) biological half-lives (days) of 13 drugs in whole egg

Drug ^a	$t_{1/2}$	$T_{1/2}$
CTC	1.6	1.6 [1.0~2.3] ^d
OTC	1.1	1.5 [1.0~2.4]
SP	2.4	1.8 [1.2~2.8]
TS	1.3	1.4 [0.9~2.2]
AMP	2.8	2.8 [1.9~4.3]
DEC	3.8	3.6 [2.3~5.6]
DTM	3.1	2.7 [1.8~4.1]
NCZ	4.2	4.2 [2.6~6.5]
PYR	2.5	2.7 [1.8~4.2]
SDD	1.1	0.9 [0.5~1.3]
SMX	0.9	0.9 [0.5~1.3]
SMM	0.9	1.0 [0.7~1.5]
SDM	1.0	1.1 [0.7~1.7]

^a For abbreviations see Table 1.^b See Table 1.^c The biological half-life in whole egg predicted from $C_{y/a}$ using Equation 2 in text.^d 95% confidence interval.

Fig. 1. Sulphamonomethoxine (SMM) contents (ppm : mg/kg) in egg yolk, albumen, and whole egg after the withdrawal. Hens were fed the diet containing 400 ppm of SMM for 5 days, thereafter, they were reared with the diet free from the drug during experimental period. SMM in egg yolk (solid circle), albumen (open circle) and whole egg (open triangle) were determined by the method described in the previous paper (FURUSAWA and MUKAI, 1995b).

egg yolk formation, follicles grow linearly in size and weight in the ovary during the final 6 d of rapid growth stage (GILBERT, 1971 a), and ovulated into oviduct to develop intact component of eggs. Consequently, a linear increase in drug content in yolk during its growth stage and a linear decrease after ovulation is expected. On the other hand, albumen is deposited only 3–10 h before shell formation (GILBERT, 1971 b). As a result, the drug content may depend on that found in blood, where many drugs decrease exponentially as reported by FURUSAWA, *et al.* (1994). Thus, the depletion profile of drug in eggs depends largely on the physiology of egg formation. The egg has a separate kinetic compartment for the drug depletion and it is independent from hen's body. Hence, it can be said that the depletion kinetics in eggs may follow its unique rules (FURUSAWA and MUKAI, 1995 b ; GEERTSMA *et al.*, 1987).

As shown in Table 1, a large variation in the content of drugs in egg yolk and albumen are found with different drugs. This variation found in the yolk and albumen may depend mainly on the lipid-solubility or water-solubility of the drug (BLOM, 1975). The drugs having the property of lipid-solubility in nature such as NCZ and PYR are found much higher content in egg yolk than those in albumen. On the contrary, those having a water-solubility, such as sulphadimidine (SDD), SMX, SMM, and SDM are found higher content in albumen than those in egg yolk.

It is noteworthy that for lipid soluble drugs, longer the biological half-lives are found in whole eggs. Again, this phenomenon may be clearly elucidated by the fact that the higher contents of drug and slow depletion are demonstrated in egg yolk. The reversed phenomena are also found in the drugs classified into those having property of water-solubility (Table 1).

These facts led us to introduce the concept that the biological half-life in whole egg may depend on the ratio of the drug contents ($C_{y/a}$) in the egg yolk to the albumen. As a result, we devised "general equation" (Equation 2) to predict biological half-lives of various drugs in whole egg using $C_{y/a}$ as the parameter. In the present study, the biological half-lives for the 13 drugs were calculated by using the "general equation". As seen in Table 2, the predicted values ($T_{1/2}$) on all drugs examined statistically consisted with those of the observed biological half-lives ($t_{1/2}$) ($P > 0.05$). Therefore, we concluded that Equation 2 can be a simple tool for describing the biological half-lives of various drugs in whole egg.

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