Residues of Veterinary Drugs in Eggs and Their Distribution between Yolk and White

Cornelis A. Kan*,† and Michael Petz‡

ID-Lelystad, Institute for Animal Science and Health, P.O. Box 65, 8200 AB Lelystad, The Netherlands, and Department of Food Chemistry, University of Wuppertal, Gaussstrasse 20, 42097 Wuppertal, Germany

Veterinary drugs and feed additives (especially some coccidiostats) can be absorbed by the digestive tract of laying hens and transferred to the egg. Physicochemical characteristics of these compounds determine their pharmacokinetic behavior and distribution to and within the egg. Traditionally the quite lipid soluble drugs and additives are expected to yield residues only in the fat-rich yolk. However, the quite lipid soluble drug doxycycline — as well as many other drugs — showed during long-term administration higher residues in white than in yolk. In a model study with 11 sulfonamides differing in pK_a value and lipid solubility, their distribution in vivo between yolk and white was determined. Neither differences in pK_a values nor those in lipid solubility could explain the distributions found. Binding to egg white macromolecules in vivo as an explanatory factor was tested with five sulfonamides, and no correlation between binding and the distribution of sulfonamides between white and yolk was found. Literature data on the distribution of drugs between egg white and yolk showed a reasonable consistency within drugs and a large variability among drugs (as could be expected). This larger database also did not provide a clue as to what factor determines the distribution of a drug between egg white and yolk when given to laying hens.

INTRODUCTION

Veterinary drugs and coccidiostats are therapeutically used for laying hens, generally by mass application via water or feed or these compounds may reach them accidentally, for example, as a result of cross-contamination in the feed mill. Some of the drugs are designed to work systemically; thus, they must cross the intestinal wall to exert their function. Other drugs — and certainly the coccidiostats — should exert their action with the gastrointestinal tract but nevertheless are (partly) absorbed. This absorption is quite logical as both veterinary drugs and coccidiostats possess certain lipophilic properties in order to interact with and pass through membranes. These lipophilic properties are a prerequisite to reach target organs or cells and to fulfill their task of eliminating microorganisms or coccidia.

When these compounds reach the bloodstream, they are distributed over the whole body. In the laying hen this includes the ovary with growing follicles and the oviduct, where the egg white is formed and secreted. The amount of the compounds or its metabolites in each tissue depends on their physicochemical characteristics.

FORMATION

Yolk. Yolk components (predominantly lipoproteins) are formed in the liver and transported via the blood to the ovary. The ovary of hens in active production contains three types of follicles at which the yolk can be deposited:

(1) Very small follicles, in the slow phase of development, which can take months or even years to develop. These are also called the white follicles as no (colored) carotenoids are deposited there.

(2) Follicles may be in the intermediate phase of growth (lasting some 60 days).

(3) Follicles may also be in the rapid growth phase, which lasts ∼10 days. The follicle weight increases during this time from some 1 g to ∼20 g. As one follicle ovulates approximately every −24 h, roughly 10 follicles are present in different stages of the rapid growth.

It is not well-known whether yolk material deposition carries on right until the moment of ovulation or if 1 day elapses between the last deposition of yolk material and ovulation. A more detailed description can be found in various textbooks on poultry physiology [e.g. Bell and Freeman (1971)].

Egg White. The (water-soluble) proteins are formed in and secreted by one part of the oviduct called the magnum. Formation of the proteins takes 1−2 days and deposition of egg white around the yolk some 2−3 h.

Shell membranes are formed in the next hour or so, and finally the deposition of the (calcium carbonate) eggshell takes place in ∼18−20 h (Bell and Freeman, 1971). This time schedule was deduced many years ago when egg production was much lower than presently achieved by highly productive hens. Therefore, it is not certain that all events still follow that time schedule. Anyway, due to these physiological processes, the pharmacokinetics of drug residues in yolk and egg white show the following common features:

(1) Residues of drugs occur first in egg white, at least when the drug is distributed toward that compartment.

(2) Residues in egg white are a reflection of plasma levels and will therefore show a constant level over time when plasma levels do. The time needed to achieve a constant level in egg white is generally 2−3 days.

† Institute for Animal Science and Health.
‡ University of Wuppertal.

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(3) Residues in yolk reflect the plasma levels during the 10 days of their rapid growth; thus, depending on the length and timing of the exposure relative to yolk growth, levels in yolk can increase, be constant, or can decrease.

(4) Residues of drugs in yolk generally require exposure for ~8−10 days to reach a constant level.

(5) A single exposure to a drug might be sufficient to detect the drug in either egg white or yolk, depending on the characteristics of the drug and the sensitivity of the analytical method used.

(6) Disappearance of drugs from white and yolk depends heavily on the plasma levels of the drug tested. Drugs that clear rapidly from the body also disappear from egg white in ~2−3 days after cessation of exposure. Disappearance of drugs from yolk generally takes ~10 days. By that time, drug-containing lipoproteins taken up during the rapid growth phase of the yolk have been excreted with the eggs.

(7) However, if the exposure level is very high and the detection limit for the drug tested very low, also residues deposited in the yolks, which are in the intermediate stage of growth, will be detectable. This can explain the fact that Arnold and Somogyi (1986) observed chloramphenicol residues in eggs until 70 days after administration. On the other hand, if the sensitivity of the method is very low compared to the residues in the egg, residues may not be detected at all or only during a very short time period.

Both Anhalt (1977) and Hafez (1991) consider the egg yolk to be the main compartment of eggs to be taken into account when considering drug residues. This in contrast to the observations of Blom (1975) — quoted by both authors — who reported much higher residues of some sulfonamides in egg white than in egg yolk.

Triggered by the observation that residues of the quite lipophilic doxycycline showed higher residues in egg white than in the (fat-rich) yolk, a systematic study with 11 different sulfonamides was carried out (Kan and Jacobs, 1998). Laying hens were exposed to sulfonamides with a range in pK_a values and lipophilicity, and the distribution in residues between egg white and yolk and the distribution between a (buffered) water phase and an organic phase were measured. No obvious (cor)-relation could be found.

This paper [an expansion of an earlier one by Kan and Rump (1992)] summarizes data from our own trials and data from the literature where exposure was sufficiently long to expect a constant residue level in egg white and yolk.

AVAILABLE DATA

The data found in the literature and from our own studies that have not been published are summarized in Table 1. They sometimes are (educated) guesses from either graphs or tables made by the first author on steady-state levels and may deviate from the data in the original papers.

GENERAL OBSERVATIONS ON THE DISTRIBUTION DATA

Sulfonamides show appreciable levels in both egg white and yolk, and with the possible exception of sulfaguanidine levels in egg white are at least equal to those in yolk, but often they are (much) higher. Tetracyclines as a group show a more divergent picture. Remarkably, the very lipophilic ones (doxycycline and minocycline) show higher levels in egg white than in (the fat-rich) yolk. The quinolones flumequin, oxolinic acid, and enrofloxacin also show much higher residues in egg white than in yolk.

Many other substances such as macrolides and nitrofuranes show diverging patterns of distribution, but in all instances levels in egg white are substantial.

Some compounds such as trimethoprim, pyrimethamine, amprolium, decoquinate, dinitolmide, and ivermectine show very low levels in egg white.

Possible Explanations. The physicochemical properties of drugs largely determine their pharmacokinetics. Martinez (1998) in a recent review pays attention to the following factors: (i) protein binding to plasma proteins as it determines availability to other compartments; (ii) molecular weight; molecules that are too bulky are not able to cross membranes; (iii) lipid solubility as measured by the octanol/water partition coefficient; and (iv) pK_a value, which determines whether a molecule is ionized at a certain pH, as according to some theories only un-ionized compounds would penetrate biological membranes.

Hafez (1991) is his review makes a distinction between drug factors, bird factors, and analytical method factors. He focuses on the yolk as the drug-containing compartment of eggs and pays no attention to residues in egg white. Anhalt (1977) also concentrates on yolk deposition processes in relation to drug residues in eggs and hardly mentions the possibility of residues in egg white.

Lipid Solubility. Lipid solubility of the drug certainly influences its deposition in the (fat-rich) yolk (Blom, 1975), but higher residues of (the lipophilic) doxycycline in egg white than in yolk (Table 1) cannot be explained in this way. Kan and Jacobs (1998) determined the distribution ratio of 11 sulfonamides between dichloromethane and buffers of pH 6.0 and 7.6. The different ratios of residues found in egg white and yolk did not correlate in that study with the measured distribution ratios between an organic phase and a water phase at either pH. Gorla et al. (1997) consider the possibility that differences in liposolubility due to a different chemical structure may alter intracellular penetration and thus explain the patterns of distribution they observed for enrofloxacin and ciprofloxacin between yolk and egg white. As ciprofloxacin is a metabolite of enrofloxacin (and thus better water-soluble), their observation that ciprofloxacin is predominantly present in yolk does not concur with this explanation.

Partitioning between Phases with Different pH Values. Distribution of drugs between compartments with different pH values according to their pK_a values has been established for a number of different combinations of compartments. Distribution between plasma and gastric juice was, for example, explained by Shore et al. (1957), that between plasma and cerebrospinal fluid by Rall et al. (1959), and intestinal absorption by Hogben et al. (1959). Schanker et al. (1964) established distribution for passage into red cells, and Atkinson and Begg (1990) predicted the distribution of drugs between plasma and milk. Kan and Jacobs (1998) compared 11 sulfonamides with a range of pK_a values. The different ratios of residues found in egg white and yolk in that comparison (see also Table 1) did not correlate with pK_a values or calculated distributions between phases with

Table 1. Literature Data on Drug Residues in Yolk and White

compound	pK_a value	content (mg/kg) in white	content (mg/kg) in yolk	ratio white/yolk	exposure method	reference
Sulfonamides						
sulfanilamide	10.5	35	43	0.81	1000 mg/L in water, 8 days	Blom (1975)
		0.15	0.14	1.07	20 mg/kg in feed, 14 days	Kan and Jacobs (1998)
sulfachlorpyrazine	5.1	0.52	0.17	3.05	50 mg/kg in feed, 14 days	Kan and Jacobs (1998)
		0.74	0.27	2.74	50 mg/kg in feed, 21 days	Kan and Jacobs, UR[a] (1998)
sulfadiazine	6.5	0.14	0.015	9.33	20 mg/kg in feed, 14 days	Kan and Jacobs (1998)
		0.64	0.15	4.27	50 mg/kg in feed, 21 days	Kan and Jacobs, UR[a] (1998)
		0.015	<0.008	>1.8	1.3 mg/kg in feed, 21 days	Tomassen et al. (1996b)
		0.04	<0.008	>5	3.8 mg/kg in feed, 21 days	Tomassen et al. (1996b)
		0.10	0.022	4.55	8.1 mg/kg in feed, 21 days	Tomassen et al. (1996b)
sulfadimethoxine	6.3	4.6	1.7	2.71	400 mg/kg in feed, 5 days	Furusawa et al. (1994)
		0.86	0.37	2.32	100 mg/kg in feed, 14 days	Kan and Jacobs (1998)
		0.40	0.18	2.22	50 mg/kg in feed, 21 days	Kan and Jacobs, UR[a] (1998)
		3.0	1.5	2	0.02% in rofenaid feed C14, 14 days	Laurencot et al. (1972)
		0.15	0.05	3	25 mg/kg in feed, 21 days	Nagata et al. (1989)
		0.25	0.1	2.5	50 mg/kg in feed, 21 days	Nagata et al. (1989)
		0.5	0.2	2.5	100 mg/kg in feed, 21 days	Nagata et al. (1989)
		0.04	0.02	2	10 mg/kg in feed, 14 days	Nagata et al. (1992)
		0.04	0.01	4	10 mg/kg in feed, 14 days	Nagata et al. (1992)
		35	12	2.92	2000 mg/kg in feed, 25 days	Onodera et al. (1970)
		35	9	3.89	5000 mg/L in water, 5 days	Roudaut (1993)
sulfadimidine	7.5	56	45	1.24	1000 mg/L in water, 8 days	Blom (1975)
		97	83	1.17	2000 mg/L in water, 8 days	Blom (1975)
		20	5	4	5 × 100 mg/kg of BW, 5 days	Geertsma et al. (1987)
		0.03	0.01	3	20 mg/kg in feed, 14 days	Kan and Jacobs (1998)
		0.16	0.03	5.33	50 mg/kg in feed 21 days	Kan and Jacobs, UR[a] (1998)
		70	30	2.33	1000 mg/L in water, 5 days	Krieg (1966)
		51	34	1.5	1000 mg/L in water, 5 days	Roudaut (1993)
		38	23	1.65	1500 mg/kg in feed, 5 days	Seib (1991)
sulfaguanidine	11.3	0.32	0.64	0.5	100 mg/kg in feed 14 days	Kan and Jacobs (1998)
		0.22	0.29	0.76	50 mg/kg in feed 21 days	Kan and Jacobs, UR[a] (1998)
sulfamerazine	7.0	0.22	0.03	7.33	100 mg/kg, 14 days	Kan and Jacobs (1998)
		23	6	3.83	2000 mg/kg in feed, 25 days	Onodera et al. (1970)
sulfamethoxazole	5.9	0.42	0.12	3.5	50 mg/kg in feed, 14 days	Kan and Jacobs (1998)
		20	1.8	11.11	2000 mg/kg in feed, 5 days	Oikawa et al. (1977)
		39	2.9	13.45	4000 mg/kg in feed, 5 days	Oikawa et al. (1977)
sulfamonomethoxine	6.0	6.8	1.5	4.53	400 mg/kg in feed, 5 days	Furusawa and Mukai (1995)
		0.20	0.04	5	25 mg/kg in feed, 21 days	Nagata et al. (1989)
		0.35	0.07	5	50 mg/kg in feed, 21 days	Nagata et al. (1989)
		1.0	0.20	5	100 mg/kg in feed, 21 days	Nagata et al. (1989)
		21	5	4.2	2000 mg/kg in feed, 25 days	Onodera et al. (1970)
sulfaquinoxaline	5.5	50	36	1.39	400 mg/L in water, 8 days	Blom (1975)
		2.3	2.0	1.15	200 mg/kg in feed, 7 days	Furusawa et al. (1998)
		0.54	0.26	2.07	20 mg/kg in feed, 14 days	Kan and Jacobs (1998)
		0.95	1.57	0.61	60 mg/kg in feed, 14 days	Nose et al. (1982)
		3.7	1.4	2.64	100 mg/kg in feed, 7 days	Petz (1993)
		80	20	4	350 mg/L in water, 3 days	Rana et al. (1993)
		3.4	2.9	1.17	500 mg/kg in feed, 12 days (intermittent)	Righter et al. (1970)
		8	2	4	400 mg/L in water, 3 days	Romvary and Simon (1992)
		8.3	2	4.15	6000 mg/L in water	Sakano et al. (1981)
sulfapyridine	8.4	<0.1	<0.005	?	50 mg/kg in feed, 14 days	Kan and Jacobs (1998)
sulfisoxazole	4.7	0.05	0.02	2.5	100 mg/kg in feed, 14 days	Kan and Jacobs (1998)
Folic acid antagonists						
ormetoprim		0.25	3.5	0.07	0.02% rofenaid in feed C14, 14 days	Laurencot et al. (1972)
trimethoprim	6.6	<0.02	0.05	<0.4	4 mg/kg in feed, 19 days	Nagata et al. (1991)
		0.02	0.25	0.08	16 mg/kg in feed, 19 days	Nagata et al. (1991)
		0.07	0.90	0.08	56 mg/kg in feed, 19 days	Nagata et al. (1991)
pyrimethamine	7.0	1.9	88	0.02	100 mg/L in water, 8 days	Blom (1975)
		<0.01	0.03	<0.3	0.1 mg/kg in feed, 21 days	Nagata et al. (1990)
		0.04	0.69	0.06	1 mg/kg in feed, 21 days	Nagata et al. (1990)
		0.13	3.3	0.04	10 mg/kg in feed, 21 days	Nagata et al. (1990)
		<0.02	0.25	<0.08	1 mg/kg in feed, 14 days	Nagata et al. (1992)
Coccidiostats						
amprolium		0.006	0.2	0.03	5 mg/kg in feed, 10 days	Kan et al. (1989)
		0.045	1.7	0.03	250 mg/kg in feed, 10 days	Kan et al. (1989)
		0.045	0.59	0.08	100 mg/kg in feed, 14 days	Nose et al. (1982)
decoquinate		0.018	0.61	0.03	40 mg/kg in feed, 14 days	Nose et al. (1982)
dinitolmide		0.15	1.57	0.09	125 mg/kg in feed, 14 days	Nose et al. (1982)
meticlorpindol		5	2.5	2	110 mg/kg in feed, 10 days	Mattern et al. (1990)
Other feed additives						
dimetridazole		0.002	0.002	1	0.95 mg/kg in feed, 21 days	Kan et al. (1995)
		0.01	0.01	1	4.7 mg/kg in feed, 21 days	Kan et al. (1995)
		0.25	0.30	0.83	3 × 50 mg/kg of BW, 3 days	Posyniak et al. (1996)
		1.2	1.4	0.86	3 × 250 mg/kg of BW, 3 days	Posyniak et al. (1996)
olaquindox		0.002	<0.001	>2	0.39 mg/kg in feed, 21 days	Keukens et al. (1996)
		0.007	0.003	2.33	1.7 mg/kg in feed, 21 days	Keukens et al. (1996)
		0.02	0.008	2.5	5.4 mg/kg in feed, 21 days	Keukens et al. (1996)

Table 1 (Continued)

compound	pK_a value	content (mg/kg) in white	content (mg/kg) in yolk	ratio white/yolk	exposure method	reference
Tetracyclines						
chlortetracycline	3.4; 7.4; 9.3	0.1	0.4	0.25	600 mg/kg in feed, 5 days	Roudaut et al. (1989)
		0.25	0.25	1	8000 mg/kg in feed, 7 days	Yoshida et al. (1973a)
doxycycline	3.5; 7.7; 9.5	0.015	<0.01	>1.5	1.1 mg/kg in feed, 21 days	Tomassen et al. (1996a)
		0.08	0.035	2.29	6.7 mg/kg in feed, 21 days	Tomassen et al. (1996a)
		0.15	0.07	2.14	11.5 mg/kg in feed, 21 days	Tomassen et al. (1996a)
		11	3.5	3.14	0.5 g/L in water, 7 days	Yoshimura et al. (1991)
minocycline	2.8; 5.0; 7.8; 9.5	0.7	0.1	7	90 mg/L in water, 4 days	Kan and Rump, UR[a] (1989)
oxytetracycline	3.3; 7.3; 9.1	1.9	2.9	0.66	2 g/L in water, 7 days	Nagy et al. (1997)
		<0.05	0.2	<0.25	400 mg/L, 7 days	Omija et al. (1994)
		0.05	0.5	0.1	600 mg/L, 7 days	Omija et al. (1994)
		0.25	0.6	0.42	800 mg/L, 7 days	Omija et al. (1994)
		0.13	0.3	0.43	0.25 g/L in water, 5 days	Roudaut et al. (1987a)
		0.15	0.3	0.5	0.5 g/L in water, 5 days	Roudaut et al. (1987a)
		0.08	<0.20	>0.4	300 mg/kg in feed, 7 days	Roudaut et al. (1987a)
		0.17	0.5	0.34	600 mg/kg in feed, 7 days	Roudaut et al. (1987a)
		0.6	0.5	1.2	2000 mg/kg in feed, 7 days	Yoshida et al. (1973b)
		0.8	1.1	0.72	4000 mg/kg in feed, 7 days	Yoshida et al. (1973b)
		0.7	1.2	0.58	0.5 g/L in water, 5 days	Yoshimura et al. (1991)
tetracycline	8.3; 10.2	0.11	0.5	0.22	0.25 g/L in water, 5 days	Roudaut et al. (1989)
		0.2	0.9	0.22	0.5 g/L in water, 5 days	Roudaut et al. (1989)
		0.17	0.9	0.19	300 mg/kg in feed, 7 days	Roudaut et al. (1989)
		0.3	1.5	0.2	600 mg/kg in feed, 7 days	Roudaut et al. (1989)
Nitrofurans						
furazolidone		0.05	0.07	0.71	100 mg/kg in feed, 28 days	Botsoglou et al. (1989)
		0.1	0.15	0.67	200 mg/kg in feed, 14 days	Botsoglou et al. (1989)
		0.2	0.25	0.8	400 mg/kg in feed, 14 days	Botsoglou et al. (1989)
		0.015	0.010	1.5	400 mg/kg in feed, 7 days	Krieg (1972)
		0.4	0.5	0.8	400 mg/kg in feed, 14 days	Petz (1984)
furaltadone		0.1	0.2	0.5	100 mg/kg in feed, 7 days	Petz (1993)
nitrofurazone	9.28	0.25	0.4	0.63	100 mg/kg in feed, 7 days	Petz (1993)
nitrofurantoin	7.2	0.1	<0.001	>100	100 mg/kg in feed, 7 days	Petz (1993)
Quinolones						
flumequin	6.25	2.1	0.3	7	90 mg/L in water, 10 days	van Leeuwen and van Gend (1989)
		9	1.7	5.29	200 mg/L in water, 5 days	Riberzani et al. (1993)
		2	0.3	6.67	5 × 12 mg/kg of BW, 5 days, oral	Samaha et al. (1991)
oxolinic acid	6.3	1.5	0.2	7.5	0.15 (0.5?) g/L in water, 5 days	Roudaut and Boisseau (1990)
		11.5	1.2	9.58	300 mg/kg in feed, 5 days	Roudaut (1998)
enrofloxacin	6.2	1.1	0.3	3.67	5 mg/kg/day in water, 5 days	Gorla et al. (1997)
ciprofloxacin	6.3	<0.15	0.18	<0.8	5 mg/kg/day in water, 5 days	Gorla et al. (1997)
Macrolides						
erythromycin	8.7	0.04 IU/g	0.12 IU/g	0.33	0.22 g/L in water, 5 days	Roudaut and Moretain (1990)
		0.1 IU/g	0.3 IU/g	0.33	0.5 g/L in water, 5 days	Roudaut and Moretain (1990)
		0.03 IU/g	0.12 IU/g	0.25	400 mg/kg in feed, 7 days	Roudaut and Moretain (1990)
		0.47	1.54	0.31	0.5 g/L in water, 7 days	Yoshimura et al. (1978)
kitasamycin	6.7	0.35	0.27	1.29	0.5 g/L in water, 7 days	Yoshimura et al. (1978)
oleandomycin		4.6	11.4	0.4	0.5 g/L in water, 7 days	Yoshimura et al. (1978)
spiramycin	8.0	2.1 IU/g	4.5 IU/g	0.47	0.4 g/L in water, 5 days	Roudaut and Moretain (1990)
		0.9 IU/g	1.3 IU/g	0.69	400 mg/kg in feed, 7 days	Roudaut and Moretain (1990)
		3	2.2	1.36	1000 mg/kg in feed 7 days	Yoshida et al. (1971)
		2.7	4.2	0.64	0.5 g/L in water, 7 days	Yoshimura et al. (1978)
tylosin	7.1	0.25 IU/g	0.6 IU/g	0.42	1 g/L in water, 5 days	Roudaut and Moretain (1990)
		5	5	1	8000 mg/kg in feed 7 days	Yoshida et al. (1973c)
		1	1	1	0.5 g/L in water, 7 days	Yoshimura et al. (1978)
Ionophores						
monensin		0.1	0.08	1.25	110 mg/kg in feed, 7 days	Keukens, Aerts, and Kan, UR[a] (1987)
narasin		0.25	0.8	0.31	70 mg/kg in feed, 7 days	Keukens, Aerts, and Kan, UR[a] (1987)
salinomycin		<0.01	1.4	<0.007	30 mg/kg in feed, 14 days	Akhtar et al. (1996)
		0.08	2	0.04	60 mg/kg in feed, 14 days	Akhtar et al. (1996)
		0.11	2.8	0.04	90 mg/kg in feed, 14 days	Akhtar et al. (1996)
		0.2	3.7	0.05	150 mg/kg in feed, 14 days	Akhtar et al. (1996)
		0.05	1.5	0.03	60 mg/kg in feed, 7 days	Keukens, Aerts, and Kan, UR[a] (1987)
		<0.01	0.22	<0.05	66 mg/kg in feed, ? days	Sambeth et al. (1985)
		<0.01	0.4	<0.02	60 mg/kg in feed, 5 days	Sinigoj-Gacnik (1996)
Anthelmintics						
flubendazole		<0.02	0.04	<0.5	2.6 mg/kg in feed, 21 days	Kan et al. (1998)
		0.02	0.11	0.18	9.4 mg/kg in feed, 21 days	Kan et al. (1998)
		0.03	0.3	0.1	27.0 mg/kg in feed, 21 days	Kan et al. (1998)
ivermectine		<0.0005	0.001	<0.5	0.11 mg/kg in feed, 21 days	Van Dijk et al. (1997)
		<0.0005	0.005	<0.1	0.36 mg/kg in feed, 21 days	Van Dijk et al. (1997)
		<0.0005	0.02	<0.02	0.76 mg/kg in feed, 21 days	Van Dijk et al. (1997)
Various						
ampicillin	2.5; 7.3	0.008	0.025	0.32	1.5 g/L in water, 5 days	Roudaut et al. (1987b)
chloramphenicol	5.5	2	10	0.2	400 mg/L in water, 10 days	Arnold and Somogyi (1986)
		0.5	1.8	0.27	400 mg/kg in feed 14 days	Petz (1984)
		0.05	0.2	0.25	200 mg/kg in feed, 5 days	Samouris et al. (1998)
		0.5	1.5	0.33	500 mg/kg in feed, 5 days	Samouris et al. (1998)
		0.5	2.5	0.2	800 mg/kg in feed, 5 days	Samouris et al. (1998)
		1.2	4	0.3	1000 mg/kg in feed, 5 days	Samouris et al. (1998)
		0.15	0.2	0.75	40 mg/L in water, 5 days	Sisodia and Dunlop (1972)
kanamycin	7.2	<0.5	1.5	<0.3	4.000 mg/kg in feed, 7 days	Yoshida et al. (1976)
		<0.5	2.2	<0.2	8.000 mg/kg in feed, 7 days	Yoshida et al. (1976)
		<0.5	4	<0.1	16.000 mg/kg in feed, 7 days	Yoshida et al. (1976)

[a] Unpublished results.

pH values of 6.0 (yolk) and 7.6 (egg white). However, the ratio of the measured distributions of the sulfonamides between an organic phase and water phases at pH 6.0 and 7.6 did correlate well with the calculated distribution of the un-ionized moiety of the drugs of a semipermeable membrane separating two watery phases of those pH values. This indicates that the pK_a values used in the calculations were about right.

Blom (1975) used the same approach to compare distribution of three sulfonamides between plasma and egg white and could not draw an unambiguous conclusion on whether this hypothesis should be accepted.

Protein Binding. Roudaut (1998) considered protein binding to be a possible explanation for the observed distribution of oxolinic acid between egg white and yolk. Gorla et al. (1997) considered the same possibility for the related compounds enrofloxacin and ciprofloxacin. Blom (1975) measured protein binding of three sulfonamides and pyrimethamine in plasma and egg white both in vitro and in vivo. Sulfadimidine had the lowest binding percentage (some 10%) and sulfaquinoxaline the highest (some 50% in egg white). The ratio of residues in egg white and yolk did, however, not differ in the same way in that study (Table 1). Kan and Jacobs (unpublished observations) also determined in vivo protein binding in egg white of five sulfonamides. Sulfachlorpyrazine and sulfadimethoxine showed binding percentages of ~30% and sulfaguanidine of ~10%. The values for sulfadimidine were quite variable between animals, but on average a binding percentage of 5% was observed. Sulfadiazine showed negative binding values, which shows that the methodology used should be considered carefully. This conclusion has been reached before, when the estimation of protein binding of oxytetracycline and doxycycline was attempted (Kan and Rump, unpublished observations). As to binding of drugs to yolk or to yolk macromolecules, neither Blom (1975) nor Kan and Rump (unpublished observations) were able to find a satisfactory methodology.

Other. Riberzani et al. (1993) suggested that the much higher levels of flumequin in egg white than in yolk might be caused by the high solubility of the "acid" drug flumequin in the basic matrix egg white. Roudaut (1998), studying the related compound oxolinic acid, also considered this a possibility to explain higher levels of both oxolinic acid and sulfadimidine in egg white than in yolk.

Diffusion from yolk to white during storage as suggested by Geertsma et al. (1987) was ruled out by Roudaut (1998) as eggs were separated immediately after laying. Distribution of doxycycline in eggs in experiments with direct separation of egg white and yolk was compared to that in experiments with prolonged storage of whole eggs, and no differences in distribution patterns were found (Kan and Rump, unpublished observations). Exchange of drugs between yolk and egg white during egg formation — especially during the 18 h of shell deposition at a body temperature of 41 °C — can, however, not be ruled out. Nevertheless, Gorla et al. (1997) consider diffusion a possibility to explain the observed distribution of enrofloxacin between yolk and egg white.

Botsoglou et al. (1989) ascribe the different distribution of furazolidone between yolk and egg white to the dissimilarity in their mode of formation in respect to the time frame, this time of formation being much longer for yolk than for egg white. This explanation might be true for drugs such as furazolidone showing higher levels in yolk, but it cannot explain how levels of certain drugs in egg white can be higher.

Other Remarkable Points. Roudaut and Boisseau (1990) could detect residues of oxolinic acid in egg white for a much longer period than in plasma and for somewhat longer period than in yolk. This does not coincide with the theory mentioned above that the levels in egg white are a reflection of levels in plasma. Van Leeuwen and van Gend (1989) observed that levels of the related compound flumequin persisted longer in egg white than in yolk. The results of these two studies suggest that quinolones might have special characteristics in combination with egg white (proteins).

The difference in distribution ratios between narasin and salinomycin is also striking. These two compounds differ only by one — uncharged — methyl group in a rather large and complicated molecule, but evidently this difference is sufficient to result in a substantial difference in distribution between egg white and yolk.

CONCLUSIONS

Drug residues will appear in both egg white and yolk after administration to laying hens. Intestinal absorption is a prerequisite for that, as transport via blood (plasma) is responsible for deposition of drugs in yolk in the ovary or egg white in the oviduct. Physicochemical properties of the drugs and the physiology of the hen and of egg formation will determine how much drug will be deposited where. At present we cannot explain or predict from variables measurable in vitro what will happen in vivo.

Some remaining points for research include the following: (1) determination of the complex or form in which drugs are transported to and deposited in the ovary; (2) determination of how and what time and place drugs enter the egg white: during deposition of egg white or (also) during plumping or even during calcification of the egg [Donoghue and Hairston (*Br. Poult. Sci.* **2000**, *41*, 174−177) meanwhile have demonstrated translocation of oxytetracycline to egg white during the plumping phase of egg formation.]; (3) determination of pH values at the microscale at those places where processes really occur and not only in the bulk of the phase; and (4) study of possible (re)distribution processes during egg and shell formation.

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