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Case Study of the Depletion of Sulfamethazine from Plasma and Tissues upon Oral Administration to Piglets Affected with Atrophic Rhinitis

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Administration of 1075 mg of sulfamethazine (SMZ)/kg of feed for 3 weeks to piglets affected with atrophic rhinitis resulted in a plasma level of SMZ during the medication period of 45 ± 6 mg/L, while the extent of N^4-acetylation (N^4-Ac-SMZ) was 10–18%. Furthermore, small amounts of a deaminated metabolite of SMZ have been detected in plasma and tissues. The half-life of SMZ in plasma was 11 h. Elimination of SMZ and N^4-Ac-SMZ from organs and tissues was rapid in the beginning, at high plasma levels ($t_{1/2}$ = 10–14 h), but was much slower at low residual levels ($t_{1/2}$ = 3–9 days). A withdrawal period of approximately 18 days should be considered in order to meet the generally accepted tolerance level for sulfonamide residues of 0.1 mg/kg.

Sulfonamide drugs are widely used for therapeutic and preventive treatment of bacterial infections caused by *Streptococcus spp*, *Staphylococcus spp.*, *Pasteurella multocida*, *Escherichia coli*, *Bordetella bronchiseptica*, or *Haemophilus spp.*

Sulfamethazine (SMZ) is commonly administered to piglets or swine in a concentration of 400 or 200 g/1000 kg of feed, respectively, for treatment of pneumonia, enteritis, or atrophic rhinitis. Atrophic rhinitis (AR), a frequently occurring disease in pigs, is characterized by atrophy of the nasal conchae and excessive space in the nasal cavity. Since the efficacy of the SMZ dosages for preventive treatment of AR has been questioned, administration of higher SMZ doses through feed to piglets and swine is not uncommon in veterinary practice.

However, information on the clinical efficacy of such a treatment and on the depletion of SMZ residues from edible tissues after medication withdrawal is limited. Therefore, a study has been performed with piglets housed on a farm with atrophic rhinitis problems, which were treated with feed containing 1075 mg of SMZ/kg for 3 weeks.

This paper reports the depletion of residues of SMZ and metabolites from plasma and tissues of diseased animals treated with SMZ under practical conditions. This information may be used for the establishment of a proper withdrawal period for the drug before slaughter.

MATERIALS AND METHODS

Twenty-seven 4–5-week-old piglets (great Yorkshire × Large White) were divided after weaning into three groups with comparable body weight, sex, and bacteriological scoring on *Pasteurella multocida* (van Leengoed and Kamp, 1986). The animals were born, weaned, and housed on a farm with a moderate degree of atrophic rhinitis. All animals received creepfeed containing 50 mg/kg apramycin for 5 days after weaning. Subsequently control group A (12 animals, 9.2 ± 2.8 kg body weight) received pelleted feed with a Cu content of 150 mg/kg. Group B (15 animals, body weights 9.5 ± 3.7 kg) received similar feed for 21 days with 1075 mg of SMZ/kg additionally. Premix, medicated, and blank feed samples contained barley, corn, soy flour, wheat, tapioca, linseed meal, calcium carbonate, dicalcium phosphate, sodium chloride, and salts of copper, zinc, manganese, and iron, as determined by microscopic analysis (*Manual of Microscopical Analysis of Feedstuffs*, 1978).

Control feed and medicated feed were analyzed for SMZ content with a simple HPLC method. Five grams of ground feed was extracted in 130 mL of boiling 0.02 M sodium hydroxide. After centrifugation, the aqueous phase was neutralized with hydrochloric acid and filtrated after further centrifugation. After addition of $NaHCO_3$, the solution was filtered and injected onto an HPLC system. A μBondapack C_{18} column (Waters Associates) was used with water/acetonitrile/acetic acid (850/75/8.5) as eluent and detection at 254 nm. With this method SMZ concentrations from 0.5 to 1500 mg/kg of feed could be determined.

In both feeds the absence of the following antibiotics, chemotherapeutics, and growth promotors was established (<2 mg/kg): Zn-bacitracine, spiramycine, virginiamycine, flavophospholipol, tylosine, monensin, avoparcine, amprolium, ethopabate, dinitolmide, dimetridazole, clopidol, decoquinate, robemidine, ronidazol, ipronidazol, methylbenzoquate, arprinocide, lasalocide, narasin, salinomycine, nicarbazin, furazolidone, nitrovin, carbadox, olaquindox, sulfadimethoxine, sulfanilamide, sulfaquinoxaline, sulfadiazine, sulfadoxine. The feeds contained approximately 50 and 0.5 mg of nitrite/kg. The following elements were determined. ICP-AAS technique: Ca (0.84%), Mg

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(0.17%), Fe (605 mg/kg), Zn (87 mg/kg), Mn (53.8 mg/kg), Cu (150 mg/kg), Sn (<0.05 mg/kg). Hydride AAS: Se (0.12 mg/kg). Cold vapour AAS: Hg (0.004 mg/kg). Graphite oven AAS: Cr (3.1 mg/kg), Ni (2.9 mg/kg), Co (0.7 mg/kg).

Pigs were fed ad libitum. Starting 2–3 weeks after birth the weight of the animals was recorded weekly as well as the total feed consumption per group during the medication period. For bacteriological investigations nasal washings and tonsil biopsies were taken prior to, during, and after the medication period (van Leengoed and Kamp, 1986).

Heparinized blood samples were collected the day before medication and two to three times at days 3, 7, 10, and 14 of the medication period. The blood was centrifuged, and the plasma and pellets were stored at −40 °C. Immediately after the last administration of medicated feed at 9.00 h of day 21 (day 0), seven animals of group A and seven of group B were transported to the Central Veterinary Institute (CDI) at Lelystad for autopsy. The remaining animals of group B were housed in a clean sty and fed with control feed. Manure was removed twice a day from the iron-slatted floors with an high-pressure gun.

Subsequently, animals of group A and B were slaughtered on days 1, 2, 4, and 9 after cessation of the medication: five animals of the control group A and two of group B on day 1 and two animals of group B on days 2, 4 and 9.

Blood and urine samples were taken, and a gross histopathological examination of the liver and the kidney was performed. From all animals of group B and from one animal of group A 100–200 g of liver, kidney, rump, shoulder, and skeletal muscle was taken, homogenized, and stored at −40 °C. Extraction, purification, and chemical analyses of SMZ, N^4-acetyl-SMZ (N^4-Ac-SMZ), and deaminated SMZ (Des-SMZ) have been performed as described previously (Haagsma et al., 1987). SMZ-glucuronide and sulfate were determined as follows: To 500 μL of plasma was added 200 μL of β-glucuronidase/arylsulphatase solution (Merck 4114), and the resultant mixture was incubated at 37 °C for 4 h. After incubation, 2 mL of perchloric acid solution (0.3 M) was added. The solution was mixed and centrifuged and to 0.8 mL of the supernatant was added 0.2 mL of sodium hydrogen carbonate solution (1.2 M). After filtration, 50 μL of the neutralized solution was injected. Meat, kidney, or liver samples were extracted ultrasonically with dichloromethane and purified and concentrated over a silica or Florisil cartridge. For SMZ and N^4-Ac-SMZ analysis HPLC on an CP™Spher C8 column was performed, using acetonitrile/sodium acetate solution as an eluent. Mean recoveries from spiked samples were 87% (muscle) and 76% (kidney) for SMZ and N^4-Ac-SMZ, and the detection limit was 0.1 mg/kg. For Des-SMZ analysis HPLC was performed on a Nucleosil 5-CN column, while identification was done by diode array UV/vis. Recovery from spiked tissue samples was 70% for Des-SMZ with a sensitivity of 10 μg/kg and 95% for plasma samples and a detection limit of 50 μg/L.

RESULTS

Concentrations of SMZ and Metabolites in Plasma and Tissues during Medication. The degree of atrophy of the nasal conchae as determined by morphological examination of a cross section of the snout (Done et al., 1982) varied among the animals but was in some cases severe (van Leengoed and Kamp, 1986).

During the medication period the average daily feed intake per treated animal was 0.54 kg, resulting in a SMZ intake of approximately 580 mg. Steady-state levels of SMZ and N^4-Ac-SMZ were reached prior to the time of the first blood sampling, i.e. 3 days after the start of the medication (Figure 1). Mean plasma levels of SMZ and of N^4-Ac-SMZ during medication were, respectively, 45 ± 6 and 7 ± 1.3 mg/L, indicating a significant extent of acetylation of SMZ.

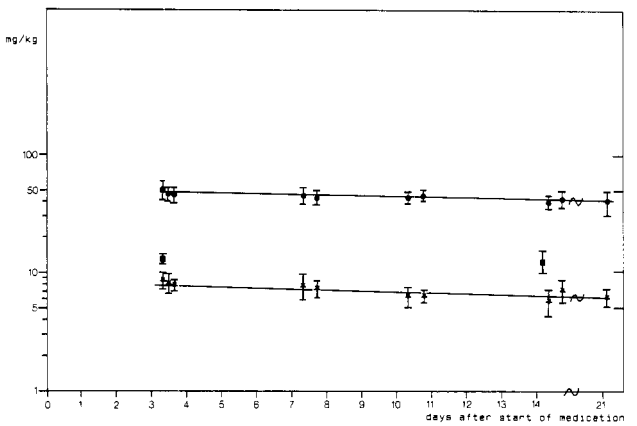

Figure 1. Concentrations of SMZ and N^4-Ac-SMZ in plasma of piglets for 21 days of feed medication with 1075 mg of SMZ/kg of feed: ●, total SMZ; *, total N^4-Ac-SMZ; ■, free SMZ (nonprotein bound).

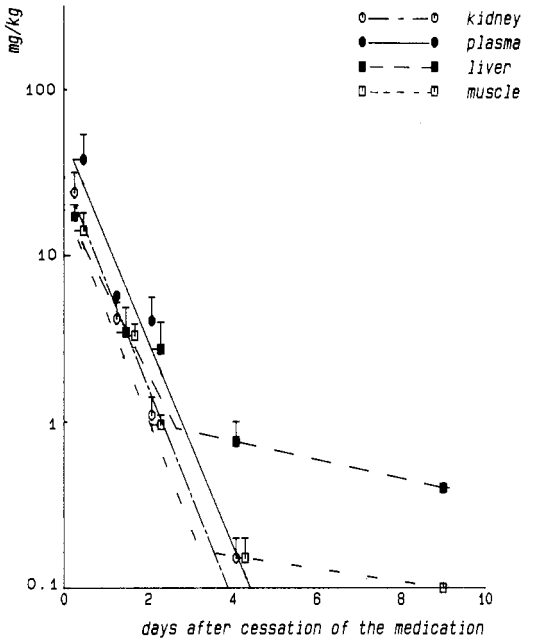

Figure 2. Time course of SMZ elimination from plasma, organs, and tissues of piglets after cessation of feed medication with 1075 mg of SMZ/kg of feed for 21 days, expressed as mean concentrations (mg/kg) and experimental variation. The number of animals analyzed at each sampling point $n = 2$, except at day 0 where $n = 6$ for plasma and kidney, $n = 3$ for liver, and $n = 7$ for rump muscle. At 30 h after medication one plasma sample was taken. The concentration of SMZ in plasma after 98 h of medication withdrawal was <0.1 mg/L.

Approximately 72 ± 9% of SMZ and 58 ± 8% of N^4-Ac-SMZ were bound to plasma proteins. Glucuronide and sulfate conjugates of SMZ in plasma amounted to 1–5 mg/L (2–10%), while no conjugates of N^4-Ac-SMZ and no 5-OH-SMZ could be detected in blood samples taken at day 14 of the medication period (<0.5 mg/kg).

Depletion of SMZ and Metabolites from Plasma and Tissues. The depletion of SMZ and N^4-Ac-SMZ from plasma, liver, kidney, and muscle after cessation of the medication is given in Figures 2 and 3, and the corre-

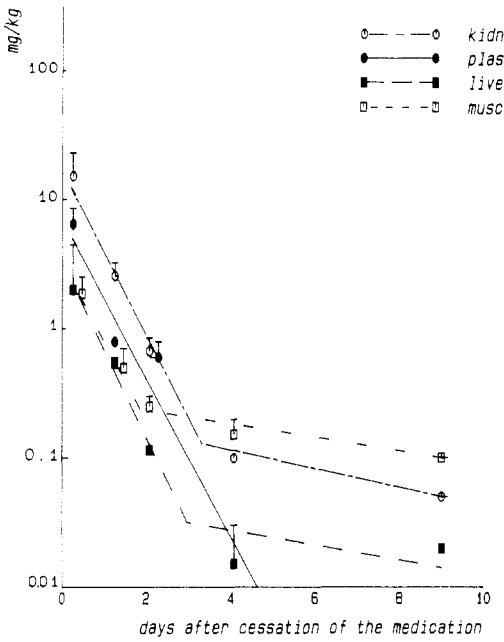

Figure 3. Time course of N^4-Ac-SMZ elimination from plasma, organs, and tissues of piglets after cessation of feed medication with 1075 mg of SMZ/kg of feed for 21 days, expressed as mean concentrations (mg/kg) and experimental variation. The same number of animals was analyzed as indicated in the legend of Figure 2. The concentration of N^4-Ac-SMZ in plasma after 98 h of medication withdrawal was <0.1 mg/L.

Table I. Half-Lives ($t_{1/2}$) of SMZ and N^4-Ac-SMZ in Plasma, Organs, and Muscle of Piglets after Cessation of Feed Medication with 1075 mg of SMZ/kg of Feed for 21 Days

	$t_{1/2}$, h			
	fast phase		slow phase	
	SMZ	N^4-Ac-SMZ	SMZ	N^4-Ac-SMZ
plasma	11	11		
liver	14	12	120	130
kidney	10	12		91
rump and shoulder muscles	12	12	204	132

sponding half-lives ($t_{1/2}$), in Table I.

Average SMZ residue levels in animals slaughtered immediately after the medication period were, in descending order, 38.0 mg/L in plasma, 23.9 mg/kg in kidney, 16.5 mg/kg in liver, and 14.2–17.7 mg/kg in muscle. Average N^4-Ac-SMZ residue levels were 6.4 mg/L in plasma, 2.0 mg/kg in liver, and 2.2 mg/kg in muscle, while the highest amount was detected in kidney, namely 15.0 mg/kg.

Furthermore, small amounts of deaminated SMZ (Des-SMZ) have been detected in plasma, liver, kidney, and shoulder muscle. Maximum levels of Des-SMZ after cessation of the medication were 1.1 mg/L in plasma, 0.2 mg/kg in liver, 0.1 mg/kg in kidney, and 0.09 mg/kg in shoulder muscle.

The concentration of SMZ in plasma and kidney dropped below 0.1 mg/kg within 4–5 days after cessation of the medication. The time dependency of the decrease could be described by a first-order process with a half-live of 10–11 h.

The time course of depletion of SMZ in liver was clearly heterogeneous. An initially rapid decrease of the SMZ concentration was observed during the first 3 days after medication withdrawal ($t_{1/2} \approx 14$ h), while at SMZ concentrations below 1 mg/kg a slow elimination process could be observed ($t_{1/2} \approx 5$ days), which resulted in a residual SMZ level of 0.4 mg/kg 9 days after cessation of the medication. A similar biphasic SMZ depletion was observed in rump and shoulder muscle. An initially fast decrease of the SMZ concentration occurred with a $t_{1/2}$ of 12 h followed by a much slower elimination rate at concentrations below 0.2 mg/kg ($t_{1/2} \approx 8$–9 days).

The time course of depletion of N^4-Ac-SMZ from plasma was approximately monophasic ($t_{1/2} \approx 11$ h). In liver, kidney, and muscle a biphasic depletion of N^4-Ac-SMZ was observed with an initially rapid decrease ($t_{1/2} \approx 12$ h) followed by a much slower elimination process ($t_{1/2} \approx 3$–6 days).

Elimination of Des-SMZ from kidney and shoulder muscle was completed within 2 days after cessation of the medication, while 9 days after medication withdrawal small amounts of Des-SMZ still could be detected in the liver (0.01–0.02 mg/kg).

DISCUSSION

Upon oral administration of SMZ to piglets affected with atrophic rhinitis a considerable extent of N^4-acetylation (15–20%) and of binding to plasma proteins (58–72%) is observed. Glucuronidation and sulfatation are minor metabolic pathways of SMZ in diseased piglets, while elimination of SMZ by hydroxylation did not occur. Similar results have been reported in the case of oral or iv administration of SMZ to 10-week-old healthy pigs (Dutch/Yorkshire breed), which resulted in a 7–13% N^4-acetylation in plasma, while 65% of SMZ and of N^4-Ac-SMZ was bound to plasma protein (Nouws et al., 1986).

This study presents evidence for the formation of small amounts of deaminated SMZ in plasma and tissues of SMZ-treated animals. Des-SMZ has also been identified in skeletal muscle, liver, and kidney of swine after administration of a single dose of 2.0 g of SMZ in 500 g of feed (Paulson and Struble, 1980; Paulson et al., 1981). Information on the mechanism of formation of deaminated sulfonamide derivatives is scarcely available. Oral dosing of rats with SMZ resulted in elevated levels of Des-SMZ in blood, liver, muscle tissue, and the gastrointestinal tract, when the diet was supplemented with nitrite (Paulson, 1986). Addition of sulfadiazine and nitrite to neonatal calves and guinea pigs also resulted in the formation of deaminated sulfadiazine.

Deaminated sulfadiazine could also be detected in guinea pigs, but not in calves, when nitrate was concomitantly administered with sulfadiazine (Woolley and Sigel, 1982). The difference in response between the animal species may be explained by the presence of nitrate reductase activity in the oral cavity of guinea pigs but not in calves. It should be reminded that the feed pellets used in our study contained approximately 50 mg of nitrate/kg, which in vivo may be reduced to nitrite. Formation of Des-SMZ may be the result of a chemical reaction since incubation of SMZ with nitrite in vitro led to a triazene compound and deaminated SMZ (Hoogenboom et al., 1987).

In a recent study by Paulson et al. (1987) it was demonstrated that SMZ in the presence of high dietary nitrite and dimethylaniline diazotized in the stomach of rats, while Des-SMZ also was formed.

The observed plasma half-life of SMZ (11 h) in piglets with conchae atrophy falls within the range of values reported for healthy animals (12–22 h) (Samuelson et al., 1979; Whipple et al. 1980; Biehl et al., 1981; Paulson et al., 1981; Nouws et al., 1986). Differences in race, age, and sex may mask a possible effect of the health status of the animal on the pharmacokinetics of SMZ in plasma. Depletion half-lives of SMZ in kidney tissue of healthy weanling pigs have been reported in the range of 27–34 h (studies cited above). The faster depletion rate of SMZ

observed in our study ($t_{1/2}$ = 10 h) may partly be due to the relatively high SMZ dosage of 1075 mg/kg of feed, which may induce subclinical nephrotoxicity in the animals. The depletion of SMZ from liver and muscle and of N^4-Ac-SMZ from kidney, liver, and muscle of the diseased piglets showed biphasic kinetic behavior with a $t_{1/2}$ (fast phase) of 10–14 h and a $t_{1/2}$ (slow phase) of 3–9 days (see Table I).

Earlier SMZ residue studies performed with healthy pigs indicated in general a monophasic depletion of SMZ from liver with half-lives of 16–36 h and from muscle with $t_{1/2}$'s of 17–31 h (Samuelson et al., 1979; Saschenbrecker and Fish, 1980; Whipple et al., 1980; Paulson et al., 1981).

The fast- and slow-elimination phase of SMZ observed in our study may be due to specific binding of SMZ or N^4-Ac-SMZ to biological receptors. At high SMZ and N^4-Ac-SMZ concentrations the binding sites become saturated and, as a consequence, unbound SMZ or N^4-Ac-SMZ will diffuse rapidly back from the tissues into the blood stream. At lower SMZ and N^4-Ac-SMZ concentrations and strong binding to receptors in the tissues, back-diffusion of the drug and its acetylated metabolite from tissues to the blood stream may become the rate-limiting process for plasma clearance. A biphasic depletion has also been described in the case of healthy weanling Yorkshire pigs fed with 100 mg of SMZ/kg of feed for 98 days (Whipple et al., 1980). A $t_{1/2}$ of 31 h was reported in muscle, while at a residual level of 0.1 mg of SMZ/kg a deviation of logarithmic linearity with the time of withdrawal was observed. The authors suggested that the slow-elimination phase may have been due to reabsorption of SMZ residues from contaminated bedding. In our study the manure was removed 2×/day after cessation of the medication, minimizing the risk of reabsorption of SMZ. Furthermore, the withdrawal feed did not contain SMZ (<0.5 mg/kg). The biphasic elimination of SMZ and N^4-Ac-SMZ as observed in this study may be a general phenomenon for veterinary drugs administered to target animals. The slow elimination occurring at low residue concentrations becomes more easily detectable today due to the rapidly increasing sensitivity of analytical detection methods.

In order to determine a safe withdrawal period for the SMZ treatment the total amount of SMZ and N^4-Ac-SMZ residues in edible organs and tissues should be taken into account since N^4-Ac-SMZ may be converted to the parent compound after oral ingestion. Since the residue concentrations of SMZ are much higher than those of N^4-Ac-SMZ in plasma, organs, and tissues of treated animals, determination of the withdrawal period should primarily be based on the depletion of SMZ residues. In the liver the residue concentration 9 days after cessation of the medication consisted mainly of SMZ (0.4 mg/kg), the N^4-Ac-SMZ concentration being 0.015 mg/kg. Extrapolation to a level below 0.1 mg/kg (a generally accepted tolerance level) results in a withdrawal period of approximately 18 days. In muscle 9 days after medication withdrawal approximately equal amounts of SMZ and N^4-Ac-SMZ were present (0.1 mg/kg). Extrapolation of the total (SMZ + N^4-Ac-SMZ) residue concentration to a level below 0.1 mg/kg results in a withdrawal period of approximately 14 days, which is somewhat shorter than the period to be observed with respect to the liver.

It is clear from this study that the depletion of SMZ and its acetylated metabolite from tissues of diseased piglets is complex and characterized by a fast- and slow-elimination phase. Further studies of the underlying molecular mechanism of this phenomena should be performed for a better understanding of drug residue depletion from food-producing animals.

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Registry No. SMZ, 57-68-1; N^4-Ac-SMZ, 100-90-3; Des-SMZ, 6149-31-1.

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