

# ブタにサルファ剤を飲水経口投与するときの適切な液量について

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# An Appropriate Ingestion Volume of Oral Sulfa Drug Suspension in Pigs

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**ABSTRACT.** The influence of ingested volume of a sulfa drug suspension, sodium sulfamonomethoxine (SMMNa), on the oral pharmacokinetics was studied in pigs, with regard to bioavailability and gastric emptying. Eighteen pigs, weighing 30–70 kg, were used. Phenol red solution was used for the evaluation of gastric emptying study. SMMNa suspension was used for pharmacokinetic study. Both of these fluids were administered by natural swallowing. Three experimental groups were constructed: G-I; 5 ml/kg of the test fluids to starved animals, G-II; 5 ml/kg of the test fluids to fed animals and G-III; 20 ml/kg of the fluids to fed animals. The glucose glycine electrolyte solution (GGES) was used as the vehicle for both the compounds. Six pigs, having duodenal cannula, were used for the study of gastric emptying. The gastric emptying rate was rapid in G-I, relatively rapid in G-III, and slow and variable in G-II. In agreement with the result of gastric emptying study, the values of  $C_{max}$  and  $t_{max}$  were high and rapid in G-I, relatively high and rapid in G-III, and low and slow in G-II. Accordingly, the voluminous ingestion of drug suspension can facilitate the gastric emptying, in turn may make the oral absorption of the drug rapid-and-uniform. The 20 ml/kg volume of sulfa drug suspension may practically be recommended for the oral administration in pigs.—**KEY WORDS:** gastric emptying study, oral pharmacokinetics, pig, solvent drag effect, sulfamonomethoxine.

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The oral route of drug administration is advisable for meat producing animals. However, unpredictable clinical effects are troublesome. They may be associated with a variable pharmacokinetics after oral drug administration [5, 6, 10]. A high  $C_{max}$ , a short  $t_{max}$  and a high-and-uniform F value are favorable for predictable clinical effects.

Sulfa drug is used worldwide in the pig industry, usually in the feed or drinking water supplement. It is rapidly absorbed from the proximal intestine. In a previous paper, we concluded that the oral pharmacokinetics of sulfa drug may be predominantly subjected to the gastric emptying in pigs [4]. In the present experiment, we evaluated several volumes of ingested volume sulfa drug suspension, examining the effects on the oral pharmacokinetics, with regard to gastric emptying.

## MATERIALS AND METHODS

*Animals and drugs:* Eighteen female commercial breed pigs (3–7 months old, Large White or Large White×Duroc) were used. Phenol red was used for the gastric emptying study. The sodium salt of sulfamonomethoxine (SMMNa, Daimeton Soda, Daiichi Seiyaku Co., Ltd., Tokyo, Japan) was used for the pharmacokinetic study. The glucose glycine electrolyte solution (GGES) was used for a vehicle for both drugs. The GGES powder of 67 g was diluted in 2 litre water. The formulation of the powder was glucose 70%, NaCl 15%, glycine 14%, citric acid 0.81%, potassium citrate 0.21% and potassium phosphate monobasic 6.8%. The osmotic pressure of the solution was 295 mOsm/kg-H<sub>2</sub>O and pH 5.6. The phenol red solution or SMMNa

suspension was administered by natural swallowing.

*Gastric emptying:* a permanent duodenal cannula (5.5 cm long, and 0.9 cm inner 1.2 cm outer diameter) was placed 20 cm from the antrum sphincter. The surgical operation of the duodenal cannula was done as described in a previous paper [4]. The recovery percentage of phenol red from the cannula was determined. The different concentration of phenol red solutions (0.01% and 0.1%) were ingested at 5 ml/kg to 2 cannulated pigs. They were starved for 24 hr before the determination. Total 6 times determinations (3 determinations in one dose in one pig) were done. The duodenal cannula was kept open for 2 hr and the effluent was collected. The concentration of phenol red and the volume of the effluent were determined. The recovery percentage was calculated.

*Gastric emptying was determined in 3 groups:* Group-I; A 5 ml/kg dose of the marker solution (0.01% phenol red in GGES) was ingested to the starved animal, Group-II; A 5 ml/kg dose of the marker solution was ingested to the fed animals, Group-III; A 20 ml/kg dose of the solution was ingested to the fed animals. The pigs of Group-II and -III were fed 2% mashed feed of body weight 30 min before the ingestion of the marker. Twelve determinations of gastric emptying were done in each group, using the 6 cannulated pigs.

Gastric emptying rate (GER) was expressed as the mean residence time in the stomach (MRT-st). The MRT-st was analyzed by the method of moment analysis on the time course of gastric emptying rate of phenol red [11].

$$\text{MRT-st} = \text{AUMC}/\text{AUC}$$

$$\text{AUMC} = \int_0^{\infty} t \cdot \text{GER} \, dt$$

$$\text{AUC} = \int_0^{\infty} \text{GER} \, dt$$

After the ingestion of the marker solution, the effluent from the duodenal cannula

was collected for 5 min, at immediately after, 0.5, 1, 1.5, 2, 3, and 4 hr and for 10 min at 6, 8, 10, 12, and 14 hr. The concentrations of phenol red and the volume of the sample were determined. The gastric emptying rate was the division of the amount of excreted marker from the duodenal cannula by the correspondent sampling time.

*Determination of quaffed volume of GGES:* The quaffed volume of GGES solution were repeatedly determined in 18 pigs. They were allowed to consume freely the GGES solution of volumes of 10 ml/kg, 20 ml/kg and 30 ml/kg after feeding the mashed feed 2% of body weight.

*Pharmacokinetic study:* The oral pharmacokinetics of SMMNa (10 mg/kg) suspension in GGES was examined in the following 3 groups. Group-I, a 5 ml/kg dose of 0.2% SMMNa suspension was ingested to the starved animals. Group-II, a 5 ml/kg dose of 0.2% SMMNa suspension was ingested to the fed animal. Group-III, a 20 ml/kg dose of 0.05% SMMNa suspension was ingested to the fed animal. The pigs of Group-II and -III were fed 2% mashed feed of body weight 30 min before the drug ingestion.

The pharmacokinetics after intravenous injection of SMMNa (10 mg/kg) was examined in all the pigs in the present experiment.

The blood was sampled from jugular vein at 0.5, 1, 3, 4, 6, 8, 12, 16, 20, 24 and 36 hr after oral or intravenous administration of SMMNa.

The concentration time data was fitted to the equation of one compartment open model. The rate constant of the terminal phase was expressed as k-term after the oral administration of drug and as  $k_{el}$  after intravenous injection. The absorption rate constant ( $k_a$ ), k-term,  $k_{el}$ ,  $C_{max}$  and  $t_{max}$  were calculated by personal computer (IF 800 Model 50, Oki Electronic Industry Co.,

Ltd., Tokyo, Japan) using the MULTI program [12]. The areas under the concentration time curve (AUC) were calculated by the trapezoidal method plus the last concentration divided by the value of  $k$ -term or  $k_{el}$ . Bioavailability was the ratio of the AUC after oral and that after i. v. injection.

A test of significance was done by the unpaired  $t$ -test.

Geometric mean was employed for the processing of the data.

*Drug determinations:* The plasma sulfonamide concentrations were determined by high performance liquid chromatographic (HPLC) analysis [4]. The HPLC apparatus consisted of a pump (LC-6A, Shimadzu Co., Ltd., Kyoto, Japan), a C8 column (Lichrosorb RP-8, 4.6  $\mu$ m $\times$ 25 cm, Gasukuro Kogyo INC., Tokyo, Japan), a UV detector (SPD-6A, Shimadzu Co., Ltd.) and a data processor (C-R4A Chromatopac, Shimadzu Co., Ltd). The mobile phase consisted of 0.05 Mol phosphate buffer (pH 4.0), methanol and acetonitril (60: 20: 5, v/v%). The flow rate was 0.6 ml/min. Plasma (0.2 ml) was deproteinized by perchloric acid. After centrifugation and filtration, 10  $\mu$ l of supernatant was injected into the HPLC system and detected at 270 nm.

The concentration of phenol red in the sample was determined by spectrophotometry [2]. The sample of the gastric emptying were centrifuged. The supernatant (0.5 ml) was mixed with 3 ml of acetone by a vibrator and allowed to stand for 20 min. The absorbance of the acetone layer at 550 nm was compared to a standard curve.

## RESULTS

The quaffed volume of GGES was determined, using 18 fed pigs, weighing 15–43 kg. All the pigs consumed 10 and 20ml/kg body weight volume of GGES solution within a minute. However, not all the pigs consumed

30 ml/kg of GGES solution.

No differences were found in the recovery percentages from the duodenal cannula between 2 doses of phenol red (Table 1). The values of MRT-st in 3 groups were presented in Table 2. The rapid and less variable gastric emptyings were found in the animals of Group-I. The relative rapid and less variable emptyings were found in those of Group-III. The gastric emptyings of those of Group-II were slow and variable.

The results of pharmacokinetic study were presented in Table 3. No statistically significant differences were found between the parameters of Group-I and those of Group-III. Statistical significant differences were found in the values of  $k_a$ ,  $k$ -term,  $C_{max}$  and  $t_{max}$  of Group-II, compared with those of Group-I. The flip-flop phenomenon was observed in the 6 animals out of 8 of Group-II. The smaller value of  $k$ -term after oral administration compared with that of  $k_{el}$  is defined as the flip-flop phenomenon.

## DISCUSSION

In the previous paper we reported that the pharmacokinetics of the sulfa drugs in pig was variable after oral administration and it may be predominantly due to the variation of gastric emptying [4]. Accordingly, the favorable pharmacokinetics, such as a high  $C_{max}$ , a short  $t_{max}$  and a high-and-uniform  $F$  value, may be expected by the

Table 1. Recovery percentages from duodenal cannula of different doses of phenol red after oral ingestion

Dose of phenol red	50 mg/kg (0.01%, 5ml/kg)	500 mg/kg (0.1%, 5ml/kg)
Recovery percentage (%)	82 (64–104)	80 (59–110)
mean (SD)		

Two pigs were used.

Three determinations in one dose in one pig.

Table 2. Mean residence time of phenol red in the stomach under 3 different experimental conditions

	Group-I (n±12) mean (SD)	Group-II (n=12) mean (SD)	Group-III (n=12) mean (SD)
AUMC (%dose time)	0.79 (0.22-2.88)	9.81* (1.75-54.8)	2.49 (1.17-5.26)
AUC (%dose)	1.67 (1.10-2.52)	1.56 (0.89-2.73)	1.33 (0.86-1.97)
MRT-st (hr)	0.42 (0.12-1.34)	4.94* (2.11-11.5)	1.72* (0.84-2.49)

$$\text{MRT-st} = \text{AUMC/AUC}$$

$$\text{AUMC} = \int_0^{\infty} t \cdot \text{GER} dt$$

$$\text{AUC} = \int_0^{\infty} \text{GER} dt$$

GER: gastric emptying rate.

\*P<0.05 compared with the value of Group-I.

Group-I: Fasting, 5 ml/kg volume of marker solution.

Group-II: Nonfasting, 5 ml/kg volume of marker solution.

Group-III: Nonfasting, 20 ml/kg volume of marker solution.

Table 3. Pharmacokinetic parameters after the oral administration of SMMNa suspension under 3 different experimental conditions

	Group-I (n=8) mean (SD)	Group-II (n=8) mean (SD)	Group-III (n=8) mean (SD)
ka (/hr)	5.23 (2.75-9.93)	1.50* (0.66-3.39)	3.62 (2.49-5.25)
k-term (/hr)	0.16 (0.12-0.20)	0.096* (0.064-0.14)	0.11 (0.081-0.15)
tmax (hr)	0.43 (0.30-0.85)	2.03* (1.01-3.65)	0.80 (0.63-1.22)
Cmax (µg/ml)	12.3 (5.09-20.00)	3.05* (1.54-5.83)	7.85 (4.63-12.5)
AUC (µg·hr/ml)	112 (89-134)	116 (81-157)	111 (86-142)
F	1.00 (0.83-1.21)	1.14 (0.77-1.60)	0.95 (0.77-1.13)

\*P<0.05 compared with the value of Group-I.

Group-I: Fasting 5 ml/kg volume of marker solution.

Group-II: Nonfasting, 5 ml/kg volume of marker solution.

Group-III: Nonfasting, 20 ml/kg volume of marker solution.

rapid gastric emptying of the drug. Gastric emptying of drug was much influenced by the stomach residue [9]. In many cases, fattening pigs are orally administered drug under the nonfasting condition. The present

experiment demonstrated that the gastric emptying of fed pig was relatively rapid and less variable by means of a voluminous ingestion of oral phenol red solution. In agreement with the result of gastric

emptying, the absorption of SMMNa was facilitated after the voluminous ingestion of the drug suspension. Also, the pharmacokinetic parameters were less variable. In conclusion, the favorable pharmacokinetics of sulfa drug can be expected by the voluminous ingestion. The sulfa drug suspension of 20 ml/kg body weight was practically recommended.

Pigs dislike an alkaline taste. The pigs, in our experiment, refused to consume a water solution of SMMNa, at a concentration of 0.1%. On the other hand, they consumed by choice SMMNa suspension in GGES, at a concentration of 0.25%. The GGES may make the sodium salt of the sulfa drug palatable. Bywater *et al.* [1] and Palmer *et al.* [8] demonstrated the solvent drag effect of GGES after oral amoxicillin in pig and after oral tetracycline and amoxicillin in cattle, respectively. The solvent drag effect explains the bulk passage of water across the intestinal membrane elicited by GGES which acts as a driving force, facilitating the drug absorption [7]. The facilitation of absorption after the oral SMMNa suspension in GGES may be secondarily due to the solvent drag effect.

Gupta *et al.* reported on the gastric emptying of water of the starved dog [3]. They observed that the oral ingestion of more than 7.5 ml/kg water caused the rapid emptying with a 1–3 min lag time. Less than 5 ml/kg body weight ingestion of water caused later gastric emptying, with a 20–30 min lag time. However, in our experiment no lag time was observed in either the starved or fed pigs after the oral ingestion of 5 ml/kg of the marker solution.

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## 要 約

ブタにサルファ剤を飲水経口投与するときの適切な液量について：小久江栄一・下田 実・鈴木里江（東京農工大学農学部家畜薬理学教室）——ブタにサルファ剤薬液を経口投与するときの適切な液量について、胃排出速度から検討した。胃排出試験ではフェノールレッドを、血中動態試験ではスルファモノメトキシンのナトリウム塩を、何れも経口補液に溶解あるいは懸濁して自由飲水させた。3つの群を設定した。第1群；5 ml/kg 液量を、絶食豚に飲ませた。第2群；5 ml/kg 液量を、採食後のブタに飲ませた。第3群；20 ml/kg 液量を、採食後のブタに飲ませた。胃排出試験の結果では、第1群の動物は早い胃排出を示した。第2群の動物は、胃排出が遅く、排出時間の変動が大きかった。第3群の動物は、比較的早い胃排出を示し、変動は小さかった。胃排出試験の結果と対応するように、第1群の動物では、サルファ剤投与後の  $C_{max}$  は高く、急速に  $t_{max}$  に達した。第2群の動物では、投与後の  $C_{max}$  は低く、 $C_{max}$  に達する時間の変動が大きかった。第3群の動物では、投与後の  $C_{max}$  は比較的高く、 $t_{max}$  に達する時間の変動は小さかった。以上から、多量の薬液を飲ませると、薬物療法に好ましい血中動態が得られる。これは薬液の胃排出が早く安定するためと思われる。採食したブタで、経口補液の飲量を調べた結果から、サルファ剤では、20 ml/kg が飲水投与に適切な液量と考えた。