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## Influence of tiamulin concentration in feed on its bioavailability in piglets

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**Summary** — Tiamulin pharmacokinetic parameters were determined in 8 2-month-old male improved Swiss Landrace piglets after intake of 2 000 mg/kg feed, 500 mg/kg feed, 12.5 mg/ml aqueous solution administered *via* a stomach tube and 180 mg/kg feed offered *ad libitum*. In all cases, the total tiamulin dose received was 10 mg/kg body weight (bw) per day. For the 2 000 mg/kg and 500 mg/kg treatments, animals were restrictively fed a commercial mix in amounts corresponding to 3-fold their maintenance requirement of digestible energy. The piglets first individually received the amount of medicated feed and immediately thereafter the rest of the daily ration. The highest tiamulin serum concentrations ( $C_{max}$ ), the largest area under the curve ( $AUC_{0-\infty}$ ), the largest absorption rate constant ( $k_a$ ), and the shortest time at which the maximum serum concentration occurred ( $t_{max}$ ) were obtained after administration *via* stomach tube followed in the respective order by the 2 000 mg/kg, 500 mg/kg and 180 mg/kg treatments. *Ad libitum* feeding of the medicated mix at 180 mg/kg failed to provide tiamulin serum concentration above minimum inhibitory concentrations (MIC) of some representative microorganisms. In conclusion, tiamulin concentration in medicated feed strongly influences its rate and extent of absorption and consequently serum concentrations. Larger tiamulin concentration in feed enhances its bioavailability. The common practice adopted by national regulatory agencies for the registration of a new drug is to conduct pharmacokinetic studies after administration *via* a stomach tube. This practice should be reevaluated because this mode of administration does not correspond to that in routine use.

**tiamulin / bioavailability / pharmacokinetics / nutrition / pig**

**Résumé** — Influence de la concentration de la tiamuline dans l'aliment sur sa biodisponibilité chez le porcelet. Les paramètres pharmacocinétiques de la tiamuline ont été déterminés chez 8 porcelets mâles de la race Landrace Suisse améliorée, âgés de 2 mois, après ingestion de 2 000 mg/kg d'aliment, 500 mg/kg d'aliment, 12,5 mg/ml de solution aqueuse, administrés par sonde oro-gastrique et 180 mg/kg d'aliment offert à volonté. Dans tous les cas, la dose totale de tiamuline

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était 10 mg/kg de poids corporel. Pour les traitements 2 000 mg/kg et 500 mg/kg, les animaux ont reçu un mélange commercial limité en quantité à 3 fois le besoin d'entretien en énergie digestible. Les porcelets ont d'abord reçu l'aliment additionné de tiamuline individuellement et ensuite le reste de la ration journalière. Les concentrations plasmiqes maximales ( $C_{max}$ ), les valeurs des aires sous la courbe des concentrations plasmiqes ( $AUC_{0 \rightarrow \infty}$ ) et les constantes de vitesse d'absorption ( $k_a$ ) les plus élevées, ainsi que les temps d'apparition de  $C_{max}$  ( $t_{max}$ ) les plus courts, ont été obtenus après 12,5 mg/ml, suivis dans l'ordre par les traitements 2 000 mg/kg, 500 mg/kg et 180 mg/kg. La préhension à volonté du mélange additionné de 180 mg/kg n'a pas produit des concentrations sériques en tiamuline supérieures aux concentrations minimales inhibitrices (CMI) pour plusieurs micro-organismes représentatifs. En conclusion, la concentration de tiamuline dans l'aliment additionné de médicament influence fortement sa vitesse d'absorption, et en conséquence les concentrations sériques. Une concentration en tiamuline plus élevée dans l'aliment entraîne une augmentation de sa biodisponibilité. La pratique du sondage oro-gastrique adoptée par les agences chargées de l'enregistrement de nouveaux médicaments devrait être réexaminée puisque ce mode d'administration ne correspond pas à l'usage de routine.

**tiamuline / biodisponibilité / pharmacocinétique / nutrition / porc**

## INTRODUCTION

The composition of feed and the feeding technique both influence the bioavailability of drugs after ingestion of medicated feed (Welling, 1989; Wanner, 1992). For example, decreased dietary calcium and increased dietary citric acid both enhance oxytetracycline and chlortetracycline bioavailability in pigs (Wanner *et al*, 1990, 1991). Also, a higher water content in the ration increases the bioavailability of various antibiotics (Sutter and Wanner, 1990; Küng and Wanner, 1993). The behaviour concerning intake of water and feed may influence drug concentration in the plasma (Rossi and Scharrer, 1992; Engeli *et al*, 1993).

Pleuromutilin with activity against Gram-positive bacteria was first identified from cultures of 2 basidiomycete strains (Kavanagh *et al*, 1951). The semisynthetic derivative tiamulin, commercially available as hydrogen fumarate, exhibits excellent *in vitro* bacteriostatic activity against *Mycoplasma* spp (Arigoni, 1962; Drews *et al*, 1975; Egger and Reinshagen 1976a,b). The therapeutic efficacy of tiamulin has been dem-

onstrated in the treatment of diseases caused by *Mycoplasma hyopneumoniae* (Goodwin, 1979; Martineau *et al*, 1980; Meszaros *et al*, 1986; Ross and Cox, 1988), *Mycoplasma hyosynoviae* (Madeiros, 1984; Burch and Goodwin, 1984), *Actinobacillus pleuropneumoniae* (Schultz *et al*, 1983; Anderson and Williams, 1990), *Streptococcus suis* type-2 (Changappa *et al*, 1990), *Leptospira pomona* (Laber and Walz, 1979), and *Treponema hyodysenteriae* (Anderson, 1983; Blaha *et al*, 1987; Olson, 1986). Under practical conditions of swine raising, tiamulin may be mixed either with feed or water (Schuller *et al*, 1977; Stipkovits *et al*, 1978; Hannan *et al*, 1982; Kobisch and Sibelle, 1982; Tomi *et al*, 1984; Burch *et al*, 1984, 1986; Pott and Edwards, 1990). Concomitant use of the ionophore antibiotics salinomycin and monensin should be avoided (Wanner, 1984; Miller *et al*, 1986).

The purpose of the present trial was to investigate the influence of the concentration of the antibiotic in the feed on the extent of enteral absorption of tiamulin. Administration of an aqueous solution of tiamulin via a stomach tube served as control.

## MATERIALS AND METHODS

### Animals and experimental design

Eight 45-d-old castrated male improved Swiss Landrace pigs with body weights of  $10.4 \pm 1.8$  (SD) kg were acclimatized to single cages with a straw-covered rubber floor. The animals originated from a specific pathogen-free herd. The temperature of the room was maintained at 24°C and humidity at 74%. After an adaptation period of 10 d, an indwelling cannula was inserted in one jugular vein under general anesthesia with halothane following im premedication with 20 mg ketamine/kg body weight (bw), acepromazine (2 mg/kg bw) and atropine (0.06 mg/kg bw) in order to facilitate blood collection. After a 3-d recovery period, the following oral dosing regimens were applied sequentially to each pig: 2 000 mg tiamulin/kg feed taken over < 5 min (d 14); 500 mg/kg feed taken over a period ranging from 13 to 22 min (d 16); 12.5 mg per ml of an aqueous solution administered *via* a stomach tube (d 18). For the 2 000 mg/kg and 500 mg/kg treatments, piglets first individually received the amount of medicated feed and immediately thereafter the rest of the daily ration. For the 2 000 mg/kg, 500 mg/kg and 12.5 mg/ml treatments, the animals were fed a pelleted commercial mix for piglets in amounts corresponding to 3-fold their maintenance requirements of digestible energy. Water was offered *ad libitum*. Fifty-five percent of the feed was given in the morning and 45% in the afternoon. In the last study phase starting at d 19 with *ad libitum* feeding, the same mix containing 180 mg tiamulin/kg was given on d 23 with free access to water. In all cases, the total dose of tiamulin received was 10 mg/kg bw per day. The medicated feed and tiamulin aqueous solution was prepared with a formulation containing 80% tiamulin hydrogen fumarate (Sandoz, Basel, Switzerland).

### Microbiologic analysis and pharmacokinetics

Blood samples were collected *via* an indwelling cannula at 0, 0.17, 0.33, 0.50, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 h for the 2 000 mg/kg, 500 mg/kg and 12.5 mg/ml treatments. Two additional samples were collected

14 and 16 h after the 180 mg/kg treatment. Tiamulin concentrations in the serum were determined by the agar diffusion test using *Sarcina lutea* ATCC 9341. The quantification limit of the assay was 0.03 µg/ml and the intra-assay variation was 2.13% ( $n = 15$ ).

Pharmacokinetic analyses were conducted with the extended least-squares non-linear regression Elsefit 1 software (Sheiner and Beal, 1985) installed on a Hewlett-Packard 1000 computer, using an open 1-compartment model. The following equation was fitted to the data:

$$C(t) = C_z \cdot e^{-\beta t} - C_1 \cdot e^{-k_a t} \quad [1]$$

where, on the ln concentration–time plot,  $C$  is the tiamulin serum concentration,  $\beta$  is the slope of the elimination phase (elimination rate constant),  $k_a$  is the calculated slope of the absorption phase (absorption rate constant),  $C_z$  and  $C_1$  are the extrapolated y-intercepts of the elimination and absorption phase respectively,  $e$  is the base of the natural logarithm, and  $t$  is the time elapsed since administration (Shargel and Yu, 1993).  $k_a$  was obtained by the Wagner–Nelson method. Pharmacokinetic parameters were subsequently derived as follows:

$$\text{Absorption half-life } t_{1/2 k_a} = 0.693 k_a^{-1}$$

$$\text{Elimination half-life } t_{1/2 \beta} = 0.693 \beta^{-1}$$

Maximum serum concentration  $C_{\max}$  = by substituting  $t_{\max}$  in Eq [1]

Time at which  $C_{\max}$  occurs

$$t_{\max} = \frac{1}{k_a - \beta} \cdot \ln \frac{k_a \cdot C_1}{\beta \cdot C_z}$$

$$\text{Lag-time } t_{\text{lag}} = \frac{1}{k_a - \beta} \cdot \ln \frac{C_1}{C_z}$$

The area under the curve (AUC) was calculated by the trapezoidal rule (Riviere, 1988a,b). AUC was extrapolated to the x-intercept ( $AUC_{0 \rightarrow \infty}$ ) using the terminal rate constant. Tiamulin availability after the 2 000 mg/kg, 500 mg/kg, and 180 mg/kg treatments was compared to that of the 12.5 mg/ml treatment (Shargel and Yu, 1993):

$$\text{Relative availability} = \frac{[AUC_{0 \rightarrow \infty}]_{\text{treatment}}}{[AUC_{0 \rightarrow \infty}]_{12.5 \text{ mg/ml}}}$$

### Statistical analysis

A block design with 4 groups of 2 litter-related pigs was used. Block effects were evaluated by the Kruskal–Wallis test using the SAS NPAR1WAY procedure (SAS/STAT *User's Guide*, 1989; Powers, 1990). Significance in paired comparisons of  $C_1$ ,  $k_a$ ,  $t_{1/2 k_a}$ ,  $C_z$ ,  $\beta$  and  $t_{1/2\beta}$  were examined by the 2-tailed Wilcoxon's signed rank test using the SAS UNIVARIATE procedure. Multiple comparisons for  $t_{max}$ ,  $C_{max}$ ,  $t_{lag}$ ,  $AUC_{0 \rightarrow \infty}$ , and  $[AUC_{0 \rightarrow \infty}]_{treatment} / [AUC_{0 \rightarrow \infty}]_{12.5 \text{ mg/ml}}$  were made with the Friedman test using the SAS FREQ procedure followed by the Wilcoxon–Wilcox test (Lozan, 1992).

### RESULTS

Tiamulin was well tolerated after application via the stomach tube, as evaluated by

physical findings. High concentrations of tiamulin in the diet did not affect the palatability of the feed. Tiamulin serum concentrations after the different treatments are presented in table I and figure 1 and pharmacokinetic parameters are listed in table II. The statistical analysis did not identify block effects. For most pigs in the 500 mg/kg and 180 mg/kg treatments, the open 1-compartment model could not be used to describe the concentration–time profiles, so all data have not been summarized in table I. The highest  $C_{max}$ , the largest  $AUC_{0 \rightarrow \infty}$  and  $k_a$  and the shortest  $t_{max}$  were obtained after the 12.5 mg/ml treatment followed by the 2 000 mg/kg, 500 mg/kg and 180 mg/kg treatments. In the case of 180 mg/kg treatment, most medicated feed was consumed during the day and serum drug concentrations decreased during the night.

**Table I.** Mean ( $\pm$  SD) tiamulin serum concentration ( $\mu\text{g/ml}$ ) in 8 piglets after intake of 2 000 mg tiamulin/kg feed, 500 mg/kg feed, 12.5 mg/ml aqueous solution via a stomach tube and 180 mg/kg feed offered *ad libitum*.

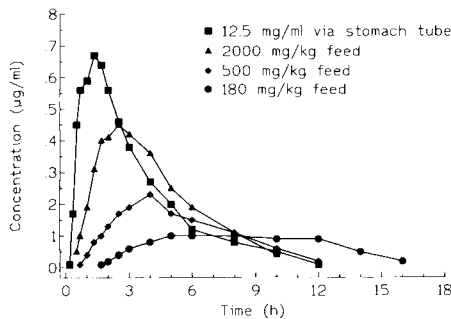
Time after beginning of intake (h)	Treatment			
	2 000 mg/kg	500 mg/kg	12.5 mg/ml	180 mg/kg
0.17	0	0	0.01 $\pm$ 0.04	0
0.33	0	0	0.17 $\pm$ 0.14	0
0.50	0.05 $\pm$ 0.05	0	0.45 $\pm$ 0.24	0
0.67	0.10 $\pm$ 0.12	0.01 $\pm$ 0.02	0.56 $\pm$ 0.28	0
1.00	0.19 $\pm$ 0.14	0.04 $\pm$ 0.05	0.59 $\pm$ 0.24	0
1.33	0.31 $\pm$ 0.19	0.08 $\pm$ 0.05	0.67 $\pm$ 0.23	0
1.67	0.40 $\pm$ 0.13	0.10 $\pm$ 0.06	0.64 $\pm$ 0.20	0.01 $\pm$ 0.02
2.00	0.41 $\pm$ 0.04	0.13 $\pm$ 0.08	0.56 $\pm$ 0.18	0.02 $\pm$ 0.04
2.50	0.45 $\pm$ 0.10	0.17 $\pm$ 0.10	0.46 $\pm$ 0.19	0.04 $\pm$ 0.04
3.00	0.42 $\pm$ 0.11	0.19 $\pm$ 0.10	0.38 $\pm$ 0.15	0.06 $\pm$ 0.04
4.00	0.36 $\pm$ 0.16	0.23 $\pm$ 0.08	0.27 $\pm$ 0.12	0.08 $\pm$ 0.03
5.00	0.25 $\pm$ 0.16	0.17 $\pm$ 0.09	0.20 $\pm$ 0.13	0.10 $\pm$ 0.03
6.00	0.19 $\pm$ 0.14	0.15 $\pm$ 0.07	0.12 $\pm$ 0.10	0.10 $\pm$ 0.04
8.00	0.11 $\pm$ 0.10	0.11 $\pm$ 0.07	0.08 $\pm$ 0.11	0.10 $\pm$ 0.04
10.00	0.04 $\pm$ 0.06	0.06 $\pm$ 0.06	0.05 $\pm$ 0.07	0.09 $\pm$ 0.06
12.00	0	[0.02 $\pm$ 0.04]	[0.01 $\pm$ 0.01]	0.09 $\pm$ 0.06
14.00	NA	NA	NA	0.05 $\pm$ 0.06
16.00	NA	NA	NA	[0.02 $\pm$ 0.06]

Values in brackets are between the detection limit and the quantification limit; NA: not applicable.

**Table II.** Tiamulin pharmacokinetic parameters (mean  $\pm$  SD) in 8 piglets after intake of 2 000 mg tiamulin/kg feed, 500 mg/kg feed, 12.5 mg/ml aqueous solution *via* a stomach tube and 180 mg/kg feed. Each pig received a total dose of 10 mg/kg bw.

Parameter	Treatment				
	2 000 mg/kg	500 mg/kg	12.5 mg/ml	180 mg/kg	
$C_1$	( $\mu\text{g/ml}$ )	3.62 $\pm$ 1.67	NA	2.60 $\pm$ 1.45	NA
$k_a$	( $\text{h}^{-1}$ )	1.42 $\pm$ 0.65 <sup>a</sup>	NA	2.80 $\pm$ 1.49 <sup>a</sup>	NA
$t_{1/2k_a}$	(h)	0.58 $\pm$ 0.25 <sup>a</sup>	NA	0.30 $\pm$ 0.13 <sup>a</sup>	NA
$C_z$	( $\mu\text{g/ml}$ )	1.62 $\pm$ 0.73	NA	1.41 $\pm$ 0.76	NA
$\beta$	( $\text{h}^{-1}$ )	0.40 $\pm$ 0.22	NA	0.42 $\pm$ 0.18	NA
$t_{1/2\beta}$	(h)	2.10 $\pm$ 0.82	NA	2.14 $\pm$ 1.29	NA
$t_{\text{max}}$	(h)	2.18 $\pm$ 0.60 <sup>a</sup>	3.81 $\pm$ 1.07 <sup>b</sup>	1.21 $\pm$ 0.46 <sup>bc</sup>	6.94 $\pm$ 3.51 <sup>ac</sup>
$C_{\text{max}}$	( $\mu\text{g/ml}$ )	0.48 $\pm$ 0.11 <sup>a</sup>	0.22 $\pm$ 0.10 <sup>b</sup>	0.69 $\pm$ 0.22 <sup>bc</sup>	0.12 $\pm$ 0.04 <sup>ac</sup>
$t_{\text{lag}}$	(h)	0.74 $\pm$ 0.28 <sup>a</sup>	0.94 $\pm$ 0.47	0.25 $\pm$ 0.11 <sup>b</sup>	2.29 $\pm$ 0.74 <sup>ab</sup>
$AUC_{0-\infty}$	( $\mu\text{g}\cdot\text{h}\cdot\text{ml}^{-1}$ )	2.23 $\pm$ 0.79 <sup>a</sup>	1.33 $\pm$ 0.67	2.50 $\pm$ 0.85 <sup>b</sup>	0.88 $\pm$ 0.40 <sup>ab</sup>
$[AUC_{0-\infty}]_{\text{treatment}}$	%	99.6 $\pm$ 52.8 <sup>a</sup>	55.4 $\pm$ 26.6	NA	39.8 $\pm$ 26.9 <sup>a</sup>
$[AUC_{0-\infty}]_{12.5 \text{ mg/ml}}$					

$C_1$  = y-intercept for  $k_a$ ;  $k_a$  = absorption rate constant;  $t_{1/2k_a}$  = absorption half-life;  $C_z$  = y-intercept for  $\beta$ ;  $\beta$  = overall elimination rate constant;  $t_{1/2\beta}$  = elimination half-life;  $C_{\text{max}}$  = maximum serum concentration;  $t_{\text{max}}$  = time at which  $C_{\text{max}}$  occurs;  $t_{\text{lag}}$  = time-lag between intake of drug and measurable drug concentration;  $AUC_{0-\infty}$  = area under the curve extrapolated to the x-intercept.  $[AUC_{0-\infty}]_{\text{treatment}}/[AUC_{0-\infty}]_{12.5 \text{ mg/ml}}$  = relative bioavailability. For treatments 200 mg/kg and 12.5 mg/ml,  $t_{\text{max}}$ ,  $C_{\text{max}}$  and  $t_{\text{lag}}$  are fitted values; otherwise they are observed. <sup>a,b,c,d</sup> identical indices indicate significant differences among means at the 0.05 level; NA: not applicable.



**Fig 1.** Mean tiamulin serum concentrations in 8 piglets after 2 000 mg/kg feed, 500 mg/kg feed, 12.5 mg/ml of an aqueous solution administered *via* stomach tube and 180 mg/kg feed offered *ad libitum*. Each pig received a total dose of tiamulin of 10 mg/kg bw.

## DISCUSSION

The following dietary factors influence the rate of gastric emptying: the composition of food (liquid, solid, fat, dietary fibers); intra-gastric volume; concentration of nutrients; salts and acidity in liquid meals; caloric content of the meal; caloric load in the intestine; and size of the food particles (Drochner, 1984; Low *et al*, 1985; Meyer, 1987; Gregory *et al*, 1990). Although the time course of solid emptying often appears to be different from that of liquid emptying, a slow, nearly linear phase predominates after both types of meals; the major differences is an initial rapid emptying phase for liquid meals. While solid food usually empties after a relatively long peri-

od of no emptying, liquid meals are discharged without or only a short initial lag. Thus, the shortest  $t_{lag}$  and  $t_{max}$  were found with the 12.5 mg/ml treatment.

In the gastrointestinal tract, weak acids and weak bases are generally not absorbed by an active mechanism (Jackson, 1987). In the case of passive diffusion, the drug concentration gradient between the lumen of the intestine and blood vessels is pivotal for the absorptive process. Thus, the high tiamulin concentration in the aqueous solution administered *via* stomach tube may account for the large values of  $k_a$ ,  $C_{max}$  and  $AUC_{0 \rightarrow \infty}$  observed after the 12.5 mg/ml treatment. However, the pharmacokinetic behavior (linearity or nonlinearity) of the tiamulin distribution and elimination processes has not been studied. It is thus impossible to rule out the influence of dose-dependent pharmacokinetics on the extent and rate of absorption.

According to the pH partition hypothesis, the weak base tiamulin is retained in an acidic medium (Ziv *et al*, 1983). Tiamulin is thus unlikely to be absorbed from the stomach, whereas the pH of the lumen of the intestine is more favorable for its absorption.

Food itself acts as a buffer. However, binding of tiamulin to dietary fibers, other macromolecules and the flora in the intestinal lumen may inhibit its absorption. Furthermore, the binding capacity of the intestinal content for water increases with increased food volume (Vahouny, 1987). The resulting shift in body water from the extracellular compartment to the intestinal lumen may contribute to the impairment of tiamulin absorption.

The MICs of *Mycoplasma hyopneumoniae*,  $\beta$ -hemolytic streptococci, penicillin- and tetracycline-resistant *Staphylococcus aureus*, and *Treponema hyodysenteriae* are 0.04, 0.04, 0.01, and 0.5  $\mu$ g/ml respectively (Drews *et al*, 1975; Hannan *et al*, 1989; Messier *et al*, 1990). *In vitro*, tiamu-

lin is bacteriostatic (Egger *et al*, 1981). *In vivo*, a deliberately chosen efficacy factor of 2–4 is applied and the MIC values correspondingly multiplied to give a minimum therapeutic concentration that should be maintained throughout treatment (Adam, 1989). For example, in the case of enzootic pneumonia, tiamulin serum concentration should be maintained  $> 0.1 \mu$ g/ml although the MIC is 0.04  $\mu$ g/ml (Drews *et al*, 1975; Goodwin, 1985; Ross and Cox, 1988). Following tiamulin application *via* stomach tube, peak serum concentrations were much higher than the MIC of these representative microorganisms. The observation of these high serum concentrations is at the origin of the generally recommended dose of 10 mg/kg bw (Laber and Schütze, 1977). However, under practical conditions where tiamulin is mixed with feed at a concentration of 200 mg active substance/kg food according to the company's guidelines, serum concentrations above the MIC of many pathogens may not be reached, especially during the night hours. These conditions correspond to the 180 mg/kg treatment. According to the regulations of national agencies for registration of new drugs for animals, it is common practice to conduct pharmacokinetic studies after drug administration *via* a stomach tube. Results of the studies are used to make recommendations for dose and withdrawal times. Because lower serum concentrations are obtained when the drug is mixed with food, therapeutic failure may ensue. The situation is further complicated in field conditions when diseased animals have a reduced appetite.

In conclusion, larger tiamulin concentration in feed enhances its bioavailability. For disease prevention and therapy, antimicrobial concentration in feed should be adequate in order to provide serum concentrations above the MIC of targeted pathogens. A smaller amount of food with a larger drug concentration followed by the

rest of the ration could be utilized when practicable, or adequate drug concentrations should be present in feed offered *ad libitum*. The choice of an optimal mode of application depends on the mechanism of antimicrobial activity (bactericidal/bacteriostatic) and the mechanism of induction of bacterial resistance. The highest tiamulin serum concentrations were obtained after administration *via* a stomach tube. The common practice adopted by national regulatory agencies for the registration of a new drug is to conduct pharmacokinetic studies after administration *via* a stomach tube. This practice should be re-evaluated, since this mode of administration does not correspond to that in routine use.

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