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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→∞}), 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 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 ...
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 plasmatiques maximales (C_{max}) des valeurs aëres sous la courbe des concentrations plasmatiques (AUC_{0-\infty}) et les constantes de vitesse d'absorption (ka) 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 Reinhagen 1976a,b). The therapeutic efficacy of tiamulin has been demonstrated 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 (Laper and Walzl, 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; Torn 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 ± 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:

\[ C(t) = C_2 \cdot e^{-\beta t} - C_1 \cdot e^{-k_4 t} \]  

where, on the ln concentration–time plot, C is the tiamulin serum concentration, \( \beta \) is the slope of the elimination phase (elimination rate constant), \( k_4 \) is the calculated slope of the absorption phase (absorption rate constant), \( C_2 \) 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). \( k_4 \) was obtained by the Wagner–Nelson method. Pharmacokinetic parameters were subsequently derived as follows:

Absorption half-life \( t_{1/2, k_a} = 0.693 k_a^{-1} \)

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

\[ t_{\max} = \frac{1}{k_a - \beta} \cdot \ln \left( \frac{k_a \cdot C_1}{\beta \cdot C_2} \right) \]

Lag-time \( t_{lag} = \frac{1}{k_a - \beta} \cdot \ln \left( \frac{C_1}{C_2} \right) \)

The area under the curve (AUC) was calculated by the trapezoidal rule (Riviere, 1988a,b). AUC was extrapolated to the x-intercept (AUC_{0→∞}) 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):

Relative availability = \[AUC_{0→∞}\]_{treatment} / \[AUC_{0→∞}\]_{12.5 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 $C_1$, $k_m$, $t_{1/2 k_m}$, $C_z$, $\beta$ and $t_{1/2\beta}$ were examined by the 2-tailed Wilcoxon’s signed rank test using the SAS UNIVARIATE procedure. Multiple comparisons for $t_{\text{max}}$, $C_{\text{max}}$, $t_{\text{lag}}$, $AUC_{0\rightarrow\infty}$, and $[AUC_{0\rightarrow\infty}]/[AUC_{0\rightarrow t_{\text{max}}}]_{12.5 \text{ mg/ml}}$ were made with the Friedman test using the SAS FREQ procedure followed by the Wilcoxon–Wilcoxon 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 $C_{\text{max}}$, the largest $AUC_{0\rightarrow\infty}$ and $k_o$ and the shortest $t_{\text{max}}$ 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 (± SD) tiamulin serum concentration (μg/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.

<table>
<thead>
<tr>
<th>Time after beginning of intake (h)</th>
<th>2 000 mg/kg</th>
<th>500 mg/kg</th>
<th>12.5 mg/ml</th>
<th>180 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.01 ± 0.04</td>
<td>0.17 ± 0.14</td>
<td>0.45 ± 0.24</td>
<td>0.56 ± 0.28</td>
</tr>
<tr>
<td></td>
<td>0.01 ± 0.04</td>
<td>0.17 ± 0.14</td>
<td>0.45 ± 0.24</td>
<td>0.56 ± 0.28</td>
</tr>
<tr>
<td></td>
<td>0.08 ± 0.05</td>
<td>0.59 ± 0.24</td>
<td>0.67 ± 0.23</td>
<td>0.64 ± 0.20</td>
</tr>
<tr>
<td></td>
<td>0.10 ± 0.06</td>
<td>0.64 ± 0.20</td>
<td>0.01 ± 0.02</td>
<td>0.02 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0.13 ± 0.08</td>
<td>0.56 ± 0.18</td>
<td>0.02 ± 0.04</td>
<td>0.04 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0.17 ± 0.10</td>
<td>0.46 ± 0.19</td>
<td>0.04 ± 0.04</td>
<td>0.06 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0.19 ± 0.10</td>
<td>0.38 ± 0.15</td>
<td>0.06 ± 0.04</td>
<td>0.08 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>0.23 ± 0.08</td>
<td>0.27 ± 0.12</td>
<td>0.10 ± 0.03</td>
<td>0.10 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>0.17 ± 0.09</td>
<td>0.20 ± 0.13</td>
<td>0.10 ± 0.04</td>
<td>0.10 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0.15 ± 0.07</td>
<td>0.12 ± 0.10</td>
<td>0.10 ± 0.04</td>
<td>0.10 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0.11 ± 0.07</td>
<td>0.08 ± 0.11</td>
<td>0.10 ± 0.04</td>
<td>0.10 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0.06 ± 0.06</td>
<td>0.05 ± 0.07</td>
<td>0.09 ± 0.06</td>
<td>0.09 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>0.02 ± 0.04</td>
<td>0.01 ± 0.01</td>
<td>0.09 ± 0.06</td>
<td>0.09 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.05 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[0.02 ± 0.06]</td>
</tr>
</tbody>
</table>

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

The following dietary factors influence the rate of gastric emptying: the composition of food (liquid, solid, fat, dietary fibers); intragastric 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 dis-
charged 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 ab-
sorbed 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 aque-
ous solution administered via stomach 
tube may account for the large values of $k_{a}$, $C_{max}$ and $AUC_{0−→∞}$ observed after the 
12.5 mg/ml treatment. However, the phar-
macokinetic behavior (linearity or nonline-
arity) of the tiamulin distribution and elimi-
nation 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 stom-
ach, whereas the pH of the lumen of the in-
testine 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 intesti-
nal lumen may inhibit its absorption. Fur-
thermore, the binding capacity of the intesti-
nal 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 hyopneumon-
iae, β-hemolytic streptococci, penicillin-
and tetracycline-resistant Staphylococcus 
aureus, and Treponema hyodysenteriae 
are 0.04, 0.04, 0.01, and 0.5 μg/ml respec-
tively (Drews et al, 1975; Hannan et al, 
1989; Messier et al, 1990). In vitro, tiamu-
lin is bacteriostatic (Egger et al, 1981). In 
vitro, a deliberately chosen efficacy factor 
of 2−4 is applied and the MIC values corre-
spondingly 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 μg/ml al-
though the MIC is 0.04 μg/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 observa-
tion of these high serum concentrations 
is at the origin of the generally recom-
manded 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 compa-
ny’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 reg-
ulations of national agencies for registra-
tion of new drugs for animals, it is common 
practice to conduct pharmacokinetic stud-
ies after drug administration via a stomach 
tube. Results of the studies are used to 
make recommendations for dose and with-
drawal times. Because lower serum con-
centrations 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 concen-
tration in feed enhances its bioavailability. For 
disease prevention and therapy, antimicro-
bial concentration in feed should be ade-
quate in order to provide serum concentra-
tions 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 reevaluated, since this mode of administration does not correspond to that in routine use.

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