Pharmacokinetics and Bioavailability of Quinidine Sulfate Following Direct Injection to the Abomasum in Healthy Cows

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Quinidine is an effective anti-atrial fibrillation (AF) drug which is often used in veterinary therapeutics, especially for horses [1]. Recently, an attempt to treat AF with quinidine sulfate was reported in high milk-producing cows [7]. When treating AF with this drug, it is difficult to maintain the expected effect due to the narrow range of therapeutic concentration. In this experiment, increasing [3] and decreasing dose methods [7] of oral administration were used. However, during these oral administration methods, large amounts of quinidine sulfate, an expensive therapeutic substance, were necessary to obtain the therapeutic concentration of plasma. Furthermore, the plasma concentration after oral administration was reported to vary extremely among test animals [6] probably due to the presence of a complex stomach [4], which sometimes causes adverse reactions (toxication). To eliminate this risk quinidine sulfate solution was injected directly into the abomasum through the body surface, and the pharmacokinetics of quinidine was analyzed. This method was expected to lead to a decrease in the amount of quinidine which is necessary to obtain a constant level of the therapeutic plasma concentration.

Five healthy non-pregnant Holstein cows, weighing between 450 and 710 kg, were used in the present study. They were judged to be healthy based on physical examination as well as routine blood chemistries (hematocrit, GPT, GOT and BUN) which tested the functions of the liver and kidney. Quinidine sulfate (1% in sterilized isotonic sodium chloride solution) was administered either into the right jugular vein or

directly into the abomasum via a needle (14–15 gage) inserted through the body surface. The criterion for successful abomasum impalement was based on the detection of gastric juice with characteristic colour, smell and low acidity. Blood (5–6 ml) was collected from the left jugular vein at 10, 15, 30, 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 12, 24 hr after administering quinidine sulfate. Blood samples containing heparin were centrifuged and the plasma was separated and stored at -30°C until an assay was made. Quinidine concentration in plasma was determined fluorometrically according to the method of Cramer and Isaksson [2]. This assay was sensitive to $0.08\text{ }\mu\text{g/ml}$ changes in plasma quinidine and the linear relationship with fluorescence intensity was obtained up to $10\text{ }\mu\text{g/ml}$ of quinidine with the recovery rate of $90.2\pm 0.7\%$ (mean $\pm$ SE, $n=70$). The concentrations of quinidine in figures and table were expressed as a free base of quinidine. The plasma concentration-time curve after administration was analyzed according to a two-compartment open model with an absorption process by using a Gauss-Newton nonlinear least squares fitting routine "MULTI" [8]. The various pharmacokinetic parameters such as half-lives of the early ($T_{1/2\alpha}$) and late phases ($T_{1/2\beta}$), apparent volume of the central (V_1) and peripheral compartments (V_2), total volume of distribution (V_{tot}), elimination rate constant (K_{el}), total body clearance (Cl_{tot}), rate constant for absorption (K_{a}) and the area under the plasma quinidine concentration (AUC) were calculated from the constant coefficients and rate constants according to Shargel & Yu [5]. The time (T_{max}) required for maximum concentration (C_{max}) of quinidine was also calculated. Bioavailability (F) was estimated by comparing AUCs obtained in intravenous and intraabomasal injections. During the experiments, the conventional clinical signs including temperature, heart and respiratory rate, and electrocardiography (ECG; Apex-Base

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Fig. 1. Plasma concentration-time profiles of quinidine following intraabomasal administration of quinidine sulfate in healthy cows. Each point represents the mean plasma concentration of quinidine after administration of 5 (○, n=4) or 10 mg/kg (●, n=5) into the abomasum. Vertical bars show S.E. Curves are expressed by the formulations of $C_p(t) = -0.11e^{-6.78t} + 3.91e^{-0.41t} - 3.81e^{-1.32t}$ at 5 mg/kg and $C_p(t) = 0.3e^{-5.95t} + 9.75e^{-0.39t} - 9.28e^{-1.31t}$ at 10 mg/kg.

Table 1. Pharmacokinetic parameters of quinidine in healthy cows after intraabomasal administration (5 or 10 mg/kg)

Pharmacokinetic parameter	Dosage	
	5 mg/kg (n=4) Mean±S.E.	10 mg/kg (n=5) Mean±S. E.
T _{1/2} α (hr)	0.109±0.016	0.118±0.071
T _{1/2} β (hr)	1.836±0.148	1.819±0.199
K ₁₂ (hr ⁻¹)	3.082±0.422	2.667±0.167
K ₂₁ (hr ⁻¹)	3.295±0.749	2.825±0.281
K _{el} (hr ⁻¹)	0.811±0.045	0.827±0.059
K _a (hr ⁻¹)	1.320±0.182	1.214±0.198
V ₁ (l/kg)	0.999±0.137	1.033±0.106
V ₂ (l/kg)	1.001±0.185	0.995±0.134
V _{tot} (l/kg)	2.163±0.364	2.198±0.260
Cl _{tot} (l/hr/kg)	0.802±0.107	0.859±0.145
F (%)	82.6 ±18.8	91.7 ±11.9
Lag time (hr)	0.427±0.118	0.404±0.062

lead) were also monitored to estimate possible toxication of quinidine. Acute quinidine toxicosis was not observed in the present study. An intraabomasal injection of quinidine sulfate was followed by the intramuscular administration of penicillin G to prevent bacteria infection.

Following intraabomasal administrations of quinidine sulfate to healthy cows, the mean plasma concentration of quinidine began to increase with a delay time of about 30 min and reached maximums of 1.40 ± 0.51 µg/ml (C_{max}) at 1.55 ± 0.23 hr (T_{max}) and 2.73 ± 0.65 µg/ml at 1.65 ± 0.23 hr in dosage of 5 and 10 mg/kg, respectively. The plasma concentration of quini-

dine then declined progressively with a similar decay rate (Fig. 1). Pharmacokinetic parameters of quinidine following intraabomasal injections were calculated using the two-compartment open model as shown in Table 1. Thus, estimated T_{1/2} β of the late phase was about 2 hr with a V_{tot} of about 2.2 l/kg in both dosages. These parameters were not dependent on the dosage of quinidine sulfate. The Cl_{tot} had a range of 0.8–0.86 l/hr/kg. These values were similar to the results observed previously in the intravenous administration by Takemura *et al.* [6]. In the intraabomasal injection, bioavailability (F) of quinidine was $82.6 \pm 18.8\%$ and $91.7 \pm 11.9\%$ in dosages of 5

Fig. 2. Plasma concentration-time profiles following repeated intraabomasal administrations of quinidine sulfate according to the simulation model. Each point represents concentration of quinidine and the solid curve shows expected plasma concentration levels as simulated by computer. The effective quinidine concentration in plasma is indicated by the range between the two horizontal lines. Initial loading dose; 20 mg/kg; Maintenance dose; 15 mg/kg; Interval of dosage; 4 hr.

and 10 mg/kg, respectively, which were about 4 times higher than that ($23.3 \pm 16.3\%$) which had been obtained in oral administration of quinidine in cows [4]. Furthermore, the variation of F among individuals was relatively small. It is generally accepted that drug preparations administered orally to ruminants must dissolve in reticuloruminal fluid and always undergo considerable dilution in the forestomachs. In the administration method adopted here this absorptive process was eliminated, since quinidine can be absorbed efficiently and rapidly. This may be a major factor in the development of high availability of quinidine. These findings may be of clinical importance, since the higher bioavailability in this method seems to save greatly the amount of quinidine sulfate required to obtain the same plasma concentration. Thus, the intraabomasal injection may be one of the effective administration routes of quinidine sulfate in cows.

It was reported that the plasma concentration of quinidine ranging from 2 to 5 $\mu\text{g/ml}$ was effective in deleting AF in cattle [6, 7]. Above 10 $\mu\text{g/ml}$ of plasma quinidine concentration, cows were observed to develop intoxication [6]. We attempted to constitute the predicted model to sustain effective plasma concentration of quinidine by intraabomasal administration for a long time. Using several pharmacokinetic parameters estimated from intraabomasal injections, the

initial dose of 20 mg/kg, the maintenance dose of 15 mg/kg and the dosing interval of 4 hrs were calculated on the basis of the expected mean plasma concentration. Figure 2 shows the predicted simulation curve and the results obtained in the experiments according to the model. In this model, an effective concentration of quinidine (2–5 $\mu\text{g/ml}$) was maintained for at least 8 hr by repeated intraabomasal administrations. The concentrations measured at several times were consistent with the predicted ones simulated by a computer (Fig. 2). McGuirk *et al.* [4] calculated the oral dose required to maintain the plasma effective concentration (more than 2 $\mu\text{g/ml}$) for 6 hrs to be 180 mg/Kg. This oral dose was 9 times higher than that for intraabomasal administration. These findings indicate that the repeated intraabomasal injection of quinidine sulfate is available in the treatment of AF, since this method provides a maintenance of safe and sufficient concentration for 8 hrs in cows.

Intoxication signs for quinidine on ECG, such as the prolongation of the PR, QRS, and QT [1], and on clinical aspects such as the impairment of the nervous system [6] were not detected during the treatment with quinidine sulfate. In some cows, slight changes such as an increase in intestinal motility, diarrhea and the separation of T phase of ECG were observed. However, they did not seem to be the adverse effects of quinidine sulfate.

In conclusion, the present study provides a possible administration method (intraabomasal injection) of quinidine sulfate offering advantages in practical economy and safety.

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要 約

成牛における硫酸キニジンの第4胃内投与後の血中動態(短報): 八村晃一・根城博一¹⁾・宮崎秀人・種池哲朗・黒沢 隆¹⁾・高橋清志¹⁾・其田三夫¹⁾(酪農学園大学獣医薬理学教室, ¹⁾獣医内科学教室)——硫酸キニジンをホルスタイン種成牛の第4胃内に直接注射した後, その血中動態を解析した。その結果, 第4胃内投与による吸収率は経口法に比べて著明に高いこと, 2回反復投与により有効血中濃度を8時間以上維持でき, かつ副作用も発現しないことを明かにした。